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American Heart Journal

84 Number 4

GEORGE E BURCH Editor

HARRY L COLCOLOUGH

JOHN H PHILLIPS Assistant Editors

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Contents on pp 3 5 and 7

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Assistant editors
HARRY L COLCOLOUGH M D
JOHN H PHILLIPS M D

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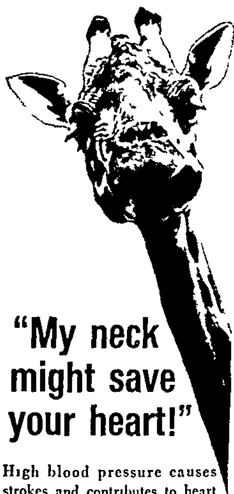
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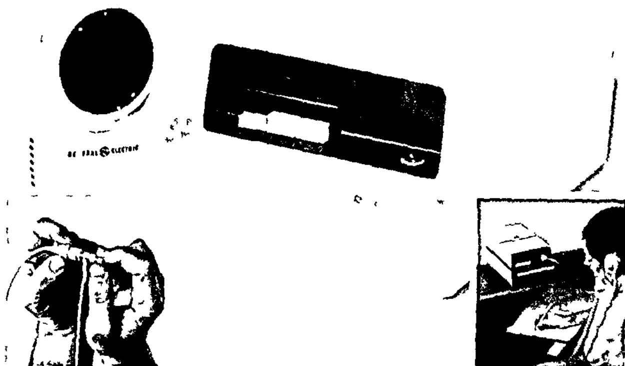


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OCTOBER 1972

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information compendium

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"The drug of choice for oral replacement of potassium is potassium chloride solution."

AMA Drug Evaluations 1971 First Edition Chicago American Medical Association p 121

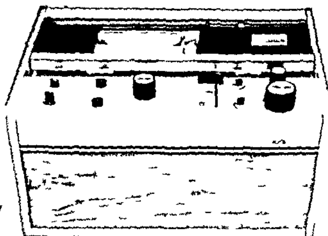
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COMPOSITION Each 15 cc (one table spoonful) contains potassium chloride 1 5 Gm supplying 20 mEq of elemental potassium in a cherry flavored palatable base alcohol 4 Contains no sugar
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CONTRAINDICATIONS Impaired renal function untreated Addison s Disease dehydration heat cramps and hyper kalemia
PRECAUTIONS Potassium chloride should be administered with caution and adjusted to the requirements of the indi vidual patient since the amount of defi ciency and corresponding daily dose is often not known Excessive or even thera peutic dosages may result in potassium intoxication Patients should be frequently checked and periodic ECG and/or plasma potassium levels ma e High plasma con centrations of potassium ion may cause cardiac depression arrhyt mias or arrest Use with caution in patients wi h cardia disease In hypokalemic states attention should be directed toward the correct on of the frequently associated hypoch oremic alkalosis
SIDE EFFECTS Vomit ng nausea abdominal discomfort and diarrhea may occur Symptoms and signs of potassium intoxication include listlessness mental confusion paresthesia of the extremit es weakness of the legs flaccid para ysis fall in blood pressure cardiac arr ythmias and heart block When hyperka emia exists it should be promptly treated w h the discor inuance of potassium adminis tration or other s eps o lower serum levels if indicated since sudden shift in plasma levels ma induce potentially dangerous card ac arrhythmias
DOSAGE AND ADMINISTRATION Adults one tablespoonful (15 cc) diluted in one glass of water twice daily after the mor g and evening meal Larger doses may be indicated according to the indi vidual patient s requirements but should be administered under close supervision due to the possibility of potassium intoxi cation Patients should be cautioned to follow directions expl citly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury
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Review of books Publishers and authors are informed that the space of the Journal is so fully occupied by matter pertaining to the branches to which it is devoted that only works treating of these subjects can be noticed Books and monographs on the anatomy physiology pharmacology therapeutics and pathology of the heart blood vessels and circulation will be reviewed when space is available Send books to the Editor Dr George E Burch 1430 Tulane Avenue New Orleans Louisiana 70112

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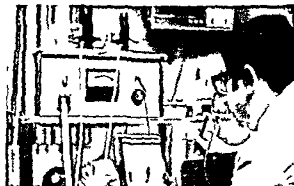
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Electrical Hazards Cardiopulmonary

New components increase lifesaving potentia

The new audiovisual components shown on this page keep the ICC Multimedia Learning System in line with current thinking on the management of coronary patients These components grew out of the recommendations of an advisory panel of experts drawn from the fields of cardiology cardiovascular nursing adult education and film production

In a field as fast changing as coronary care the Multimedia Learning System thus provides a means by which hospital staffs can be kept abreast of current developments Not only ICCU nurses but all medical and paramedical personnel will benefit from such presentations as Electrical Hazards and Cardiopulmonary Resuscitation



Preventing electrical hazards Paradoxically every lifesaving electrical device in the ICCU can also be a potential killer The new filmstrip demonstrates how patient and nurse are both parts *of an electrical environment and shows how accidents can be* prevented by routine safety precautions



An efficient, integrated system

The Multimedia Learning System starts with the most advanced educational techniques then coordinates and interrelates *these techniques so* that one reinforces another to form an integrated teaching *system*

Under the over all guidance of a nurse instructor motion pictures sound filmstrips audiotapes texts lectures demonstrations and clinical experience all work together to enhance the efficiency of the learning process And because so much of the course content is on film and filmstrips physician and nurse instructors do not have to prepare the same material anew for each incoming group Relieved of repetitive preparations they can spend more time on discussions demonstrations and bedside teaching

Understanding Arrhythmias Each of four new filmstrips covers one group of arrhythmias classified by site of origin analyzes several types in each group and explains identification Practical problem solving exercises then relate the arrhythmia to the patient s history clinical condition and treatment

Handling cardiopulmonary resuscitation Successful cardiopulmonary resuscitation demands both a high level of training and an understanding of the physiological processes involved The new *filmstrip prepares the ICCU nurse for the judgments she must* make and trains her in administering CPR either alone or as part of a team



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American Heart Journal

October 1972 Volume 84 Number 4

Editorial

Concerning the etiology of congenital cardiac disease

Herbert D Ruttenberg MD
Salt Lake City Utah

Medicine today is involved in a massive assault on the prevention and cure of cancer and acquired heart disease but very little effort is being expended to prevent congenital defects Yet there are valid reasons for increasing our efforts in this area Congenital malformations not only occur frequently but they are important because they are often life threatening cause a great deal of physical and psychological harm to the affected person and his family and may be very costly in the over all management Clinically significant congenital defects are more common than is generally realized and cardiac malformations account for a high percentage of the total[1-4] Campbell[1] for instance reported a 2 4 per cent incidence of major congenital malformations in a review of British families studied and cardiac anomalies accounted for one fourth of these defects

While there are a wide variety of congenital cardiac malformations about 85 per cent of these malformations are made up of a relatively small number of lesions The most common lesion by far is ventricular septal defect with a reported incidence of 20 to 40 per cent The other common lesions are patent ductus arteriosus atrial septal defect coarctation of the aorta pulmonary valvular stenosis aortic valvular stenosis tetralogy of Fallot and complete transposition of the great vessels It is logical that the prevention of some or all of the more common lesions would therefore greatly reduce the problem of congenital cardiac defects But to prevent congenital malformations it is first necessary to understand their etiology and pathogenesis

While there exists a mass of information on the clinical aspects of congenital cardiac disease very little is known about the etiology except that there are likely to be multiple factors involved[4] It is estimated that in only one fifth of these cases is the etiologic factor known or strongly suspected The major known etiologic factors are environmental (virus infections radiation and perhaps drugs) and genetic (familial or hereditary and chromosomal abnormalities)

The importance of genetic factors in the etiology of congenital cardiac disease has been summarized by Campbell[1] Siblings of propositi (the affected persons) have three times (1 7 per cent) the expected incidence of congenital cardiac disease and this rate varies with the type of lesion There is also a strong tendency for concordance of lesions in siblings of propositi The incidence of congenital cardiac mal

From the Departm t of Pediatrics, D iso f Ped tri C d logy U rsity of Utah Colleg f Med ci e S lt Lak City Ut h.

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augments the effects of other diuretics— combined with another diuretic Dyrenium can augment diuresis and natriuresis with lower doses of each agent [2]

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Warnings *Observe regularly for possible blood dyscrasias* liver damage or other idiosyncratic reactions Blood dys crasias have been reported Check BUN and serum potas sium periodically especially in the elderly diabetics and those with suspected or confirmed renal insufficiency Use in pregnancy only when essential to patient welfare Dyrenium (triamterene SK&F) and spironolactone are not usually used concurrently *if they are* however frequent serum potassium determinations are required

Precautions If hyperkalemia develops withdraw the drug The following may also occur electrolyte imbalance low salt syndrome (with low salt intake) reversible mild nitrogen retention decreasing alkali reserve with possible metabolic acidosis Do periodic hematologic studies in cirrhotics with splenomegaly Concomitant use with anti-hypertensive drugs may result in an additive hypotensive effect When *Dyrenium is to be discontinued* after in tensive or prolonged therapy withdraw gradually because of possible rebound kaliuresis

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Note When combined with another diuretic the initial dosage of each agent *should be lower than recommended*

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1 Ross E J Aldosterone and Its Antagonists *Clin Pharmacol & Therap* 6 65 (Jan Feb) 1965
2 Earley L E Edema Formation and the Use of Diuretics *California Med* 114 56 (Mar) 1971

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not be closed at birth and small ventricular septal defects are frequently noted in the early neonatal period These defects usually close spontaneously within the first year of life Two explanations for this phenomenon are (1) that delayed closure of the ventricular septum is a natural event or (2) that a teratogenic agent interferes with closure causing either delay or complete arrest The reason for this speculation is to suggest that investigation of the pathogenesis of congenital cardiac disease should involve all periods of gestation

From a simplistic point of view prevention of congenital cardiac disease will be possible when the basic mechanisms of the various etiologic agents are understood It is obvious from Overall s review[9] (to be published in a forthcoming issue) of just one etiologic agent the virus that the task is enormous In this paper the reader is offered an up to-date thorough review of the virus as an etiologic agent in congenital cardiac disease Overall rigorously evaluates the current information on the role of intrauterine viral infections and proposes areas of investigations which may be most profitable in working out the pathogenesis and prevention of viral induced congenital cardiac anomalies

It is very attractive to consider viruses as possible etiologic factors in the production of congenital cardiac defects In many ways viruses meet the criteria for an ideal teratogenic agent Viruses are ubiquitous infect humans repeatedly with benign maladies such as respiratory and gastrointestinal infections and are frequently mild or subclinical Many viruses enter the blood stream during the course of an infection and thus may be carried to the placenta Viruses enter cells and disturb cellular processes to varying degrees Viruses also show a special affinity for fetal cells

In spite of the intriguing properties of viruses mentioned above Dr Overall[9] points out many problems in establishing the virus as a major etiologic factor in congenital cardiac disease He points out that in most instances virus infections are apparently not associated with viremia and are therefore no threat to the fetus Further more even when viremia is present the placenta may act as a barrier to fetal infection Epidemiological methods are fraught with difficulties and have not been as rewarding as had been hoped And finally there is not as yet an adequate mammalian model for the study of virus induced congenital cardiac disease

Overall s[9] critical discussion of the data on each virus thus far implicated as a possible etiologic agent makes it clear that the rubella virus is still the only virus proved to be a cardiac teratogen in humans Despite its minor role as an etiologic agent continued investigation of its interaction with the cell may provide clues to the mechanism of other etiologic factors For example the rubella virus is usually noncytolytic and allows cell growth but this growth is then often abnormal There is evidence that rubella virus causes growth retardation of cell masses and may produce chromosomal damage and affect DNA production It is obvious that these virus induced cellular changes in an embryo could be responsible for abnormal organogenesis And if rubella virus can cause cardiac malformations why cannot other viruses do the same?

After a careful reading of Overall s review[9] one is left with conflicting feelings On the one hand evidence to date suggests that viruses are only minor etiologic factors in the production of congenital cardiac defects On the other hand a better understanding of basic mechanisms of virus cell interaction may lead to the discovery of pathogenetic mechanisms of other etiologic factors and eventually to methods of prevention The characteristics of viral cell interaction seem to offer optimal conditions for environmental teratogenesis Perhaps future investigations will prove that virus agents are indeed a more important factor in teratogenesis than our present knowledge allows us to assume

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formation in the children of propositi is 4.4 per cent or 7 times the normal incidence and consanguinity increases the incidence in their offspring. The striking relationship between chromosomal abnormalities and congenital cardiac malformations leaves no doubt as to the etiologic importance of genetic mechanisms. Trisomy 21, for example, is associated with a 40 per cent incidence of cardiac anomalies, 50 per cent of which are a form of endocardial cushion defect. Heredity is also an important factor as exemplified by the familial occurrence of cardiomyopathies, situs inversus (autosomal recessive), and atrial septal defect (autosomal dominant with varying penetrance). The data on twins, however, has clouded the issue with regard to genetic factors. The incidence of congenital cardiac disease in the twins of propositi is reported to be the same as the incidence of such disease in the general population, and there is no difference in concordance between monozygotic and dizygotic twins.[6,7] Nora and co-workers, however, found a significant concordance of congenital cardiac malformations in identical twins.[7a] Since genetic mechanisms are proved etiological factors in congenital cardiac disease, the evidence from studies of twins suggests that other factors are necessary, acting together with genetic propensity to effect the production of cardiac malformations. Campbell[1] defends this hypothesis by citing examples in which the effects of certain teratogens depend on the genetic makeup of the animals tested.

While there may be many etiologic factors in congenital cardiac disease, the mechanisms by which they alter the formation of the heart are poorly understood. DeHaan[8] believes there is currently sufficient knowledge of embryology and genetics to approach this subject experimentally. The process of embryogenesis occurs by three means: growth (mitosis), differentiation, and morphogenesis. The primitive cell behaves in a certain manner because of "information" coded into its genome and because of environmental influences. When seeking the causes of abnormal embryogenesis, it is therefore necessary to answer the following questions: (1) Which of the three fundamental processes (mitosis, differentiation, or morphogenesis) is primarily influenced? (2) To what extent is the developmental event controlled by environmental influence upon the cell? (3) To what extent does the genetic makeup of the cell alter the effects of environmental influences?

Considering the importance of understanding the mechanisms involved in the production of congenital cardiac disease, it is very discouraging to find a paucity of active research in this field. Most of the literature deals with the application of teratogenic agents early in embryogenesis and the defects produced are complex. Very little data are available on the production of the common cardiac defects such as ventricular septal defect. DeHaan[8] in 1966 stated that, to his knowledge, "there is not a single laboratory in this country or elsewhere where experiments are being performed to test whether the fundamental process responsible for closure of the intraventricular foramen is mitosis, cell migration, adhesion, or death of the cells involved, nor is anyone investigating how a particular genotype or a virus might disturb these processes to yield such a defect."

Another question which needs to be answered is: At which stage of gestation does an etiologic agent act to produce congenital cardiac malformations in human beings? It is a popular belief that a teratogenic agent must have its effect during the first six to eight weeks of gestation, since by the end of that period the formation of the heart is complete. This belief is supported by data on the rubella virus. Rubella infection of the fetus in the first trimester accounts for the vast majority of congenital cardiac defects produced by this agent. While early gestational action of teratogenic agents may be a requirement to produce complex cardiac malformations (maldevelopment of the conotruncus and endocardial cushion), this may not be the case for the more common lesions such as ventricular septal defect, patent ductus arteriosus, aortic and pulmonary valvular stenosis, and coarctation of the aorta. It is entirely possible that teratogenic agents such as viruses may alter valve leaflets, cause constricting lesions to develop, and delay closure of the ventricular septum and ductus arteriosus at any stage of gestation. The ventricular septum, for example, may

Clinical communications

The relationship of the jugular "C" wave to changing diastolic intervals

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Early in this century the jugular C wave attracted the interest of many noted physicians Mackenzie[1,2] Morrow[3,4] and Hirshfelder[5] carried on a lively debate concerning its origin Two theories were popular Mackenzie and Wood[6] many years after him regarded the jugular C wave as being caused by the systolic pulse from the carotid and subclavian arteries Morrow Hirshfelder and Potain[7] maintained that the wave was a consequence of right ventricular contraction and tricuspid valve closure

In a recent paper from this laboratory we showed that the jugular C wave occurs significantly earlier than the rise of the carotid pulse in patients with left bundle branch block[10] We concluded that the jugular C wave was not of carotid origin but were unable to make any statement on where it does originate To investigate this further we examined the jugular C wave in patients with atrial fibrillation to determine the effect of cycle length on its amplitude

If the C wave were due to tricuspid valve movement it should increase with shorter cycles due to greater tricuspid valve excursion This would also provide further confirmation that the C wave is not of arterial origin since the arterial pulse increases with longer cycles

Methods

Phonocardiograms with good quality jugular venous pulse recordings were obtained on 14 patients with atrial fibrillation and various types of heart disease just prior to diagnostic cardiac catheterization We examined records of eight patients with predominant mitral stenosis four patients with atrial septal defect two patients with mitral and tricuspid stenosis one patient with a repaired atrial septal defect and one patient with idiopathic atrial fibrillation We measured the R R interval and the C wave height which is expressed as a percentage of the total excursion of the jugular venous pulse The total excursion was measured from the peak of the C wave to the nadir of the Y descent

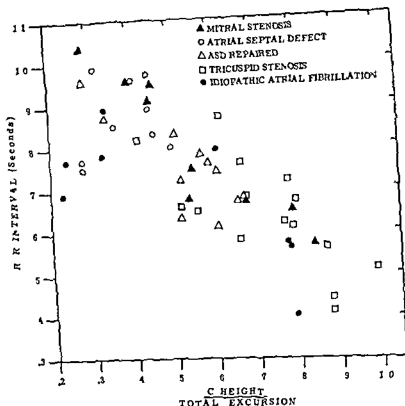
Jugular pulses were recorded by the method described by Tavel[8] A funnel shaped pickup device with an open end

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F 2 Graph of C wave height/total ju lar pul e excursion against R R interval for various types of heart disease with atrial fibrillation. The C wave hei ht is enhanced with shorter cycles

plotted The correlation coefficient is −0 78 which is significant at the 0 01 level All patients included in the study showed augmentation of the jugular C wave with decreasing cycle length only five are plotted for simplicity of presentation

Fig 3 shows an echogram of the tricuspid valve in a patient with atrial fibrillation and atrial septal defect The excursion of closure increases with shorter R R intervals We attempted to obtain echograms of the tricuspid valve in other patients in the study but the technique is difficult and adequate tracings were not obtained

Discussion

There have been numerous theories proposed as the mechanism of production of the jugular C wave These have been reviewed in a recent paper from this laboratory and will not be enumerated in detail [10]

Hartman in 1960 observed that with longer cycle lengths the C wave tended to diminish Our findings document this observation It is interesting to note that Wood [8] in the second edition of *Diseases of the heart and circulation* while stating that the C wave of external jugular phlebograms represents the carotid pulse itself includes on the preceding page a right atrial pressure tracing which shows noticeably larger C waves with shorter cycles He makes no mention of this in the text

There are two separate waves visible in the jugular pulse according to Coleman[1]—an A V wave which is caused by tricuspid closure and a C wave of carotid origin By our method of recording however we seldom see the later wave and can make no statement regarding it.

If the C wave which we record were a consequence of right ventricular contraction alone as Hartman[11] and others have held we would expect the C wave to enlarge with longer diastolic filling periods and a more vigorous subsequent contraction Our data do not support this

Our observations however do support

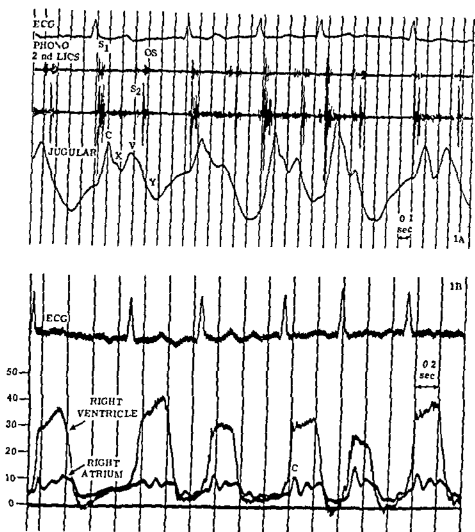


Fig. 1. Changing C wave height with cycle length. The C wave is larger with shorter cycles in both right atrial and jugular venous pulse tracings. The C wave is particularly large in the third and fourth cycles in the jugular tracing and in the fifth cycle of the right atrial tracing. The patient had a prosthetic mitral valve with tricuspid insufficiency and mild tricuspid stenosis.

(2.5 cm. in diameter) is held over the internal jugular vein usually about 1 cm. above the clavicle and 1 cm. to the right of the sternocleidomastoid muscle. The open end of the funnel is then angled downward toward the diaphragm at approximately 45°. Tracings were recorded during held expiration in the recumbent position with the head elevated on one pillow. The funnel was connected to a piezoelectric microphone (Sanborn No. 374). The electrical signals were recorded graphically with an Electronics for Medicine Recorder (Model DR 8). The incoming signals were filtered with a band pass filter set at a range of 0.1 to 20 cycles per second (c.p.s.). Recording speed was 100 mm. per second and time lines were set at 0.1 second intervals.

Adequate right atrial pressure curves were available for eight of the 14 patients. On one patient an echocardiographic recording of the tricuspid valve was available. The multichannel strip chart recording technique as described by Tavel and associates[9] was used in recording the echogram.

Results

Fig. 1 is a jugular venous pulse tracing and right atrial and right ventricular pressure tracing in a patient with mild tricuspid stenosis and insufficiency which illustrates a noticeable increase in C wave amplitude with short cycle lengths.

Fig. 2 is a scattergram comparing R-R interval with C wave height expressed as a percentage of the total excursion of the jugular pulse for each cycle. One patient with each of the types of heart disease was

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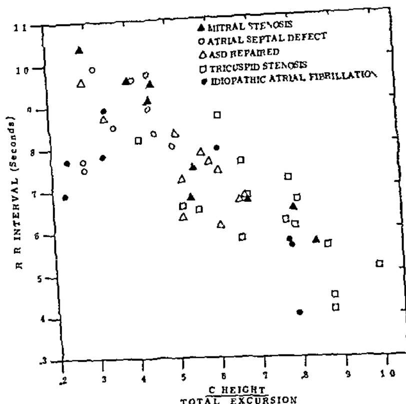


Fig 2 Graph of C wave height/total jugular pulse excursion against R R interval for various types of heart disease with atrial fibrillation. The C wave height is enhanced with shorter cycles

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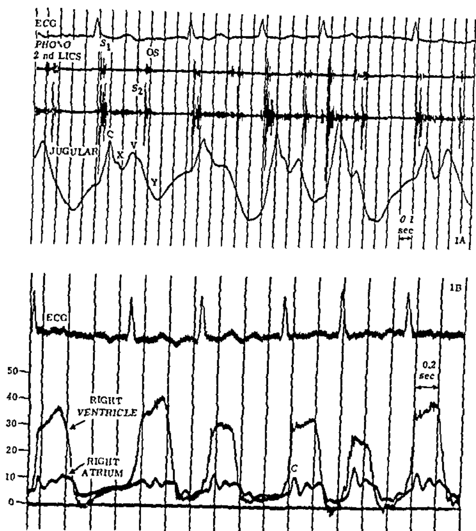


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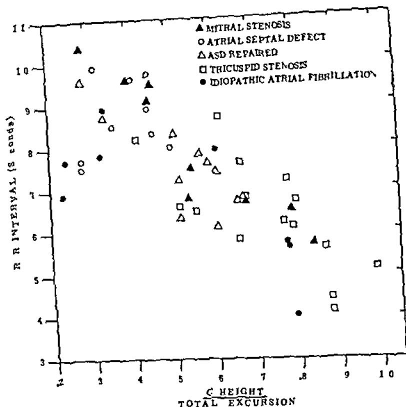


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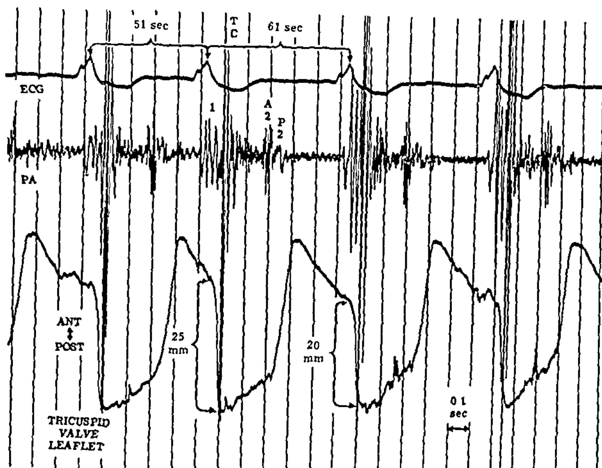


Fig 3 Echogram of *tricuspid leaflet in a patient with atrial septal defect With shorter cycles the excursion of* closure is greater

the theory that the C wave is due to tricuspid valve movement The C wave amplitude varies directly with the expected excursion of closure The excursion of closure is expected to be greater with shorter cycles since the leaflets would be more widely open in early diastole This is con*firmed with an echogram of the tricuspid* valve (Fig 3) It is also possible that the tricuspid leaflet may be allowed to bulge into the atrium following shorter diastoles because of the smaller systolic volume and relative longer lengths of the chordae supporting the valve thus giving a larger C wave

Our findings not only confirm the work of Rich and Tavel Morrow and others deny*ing the arterial origin of the C wave* but strongly suggest that Potain's theory of tricuspid origin is indeed correct

Summary

To determine the relationship of the jugular C wave to changing cycle length jugular pulse and right atrial pressure recordings were examined on a group of patients with various types of heart disease and atrial fibrillation The total height of *the jugular C wave was noted to* be enhanced by short cycles and diminished with longer cycles This finding is confirmed with intra atrial pressure recordings

It is suggested that the jugular C wave is related to tricuspid leaflet excursion and closure in that with a short diastolic interval *the leaflets are widely separated* at the onset of systole and have a relatively large closure excursion These findings are not consistent with the hypothesis of arterial origin of the C wave since the arterial pulse would be expected to increase with longer cycles

The authors wish to thank Mrs Jane Stewart for invaluable technical assistance

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Cardiac deterioration replacing cardiac pain after surgery to revascularize the heart

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Herein are reported three cases to illustrate that cardiac deterioration can replace cardiac pain after operations intended to revascularize the heart. Some possible mechanisms underlying this paradoxical result are discussed.

Case reports

Case 1. J. B., a 59-year-old white man, was first seen at Temple University Health Sciences Center in October, 1969. Four years previously he had developed an ache in both wrists while dancing. Shortly thereafter he experienced pain in both arms while walking. Later, pain radiated from both arms to the interscapular region, over both shoulders to the sternum and precordium. The number of attacks of pain a day increased and interrupted his work as a warehouse worker. At first pain was relieved by one or two nitroglycerin tablets but later the pains became so severe and so frequent that he required as many as fifty to one hundred nitroglycerin tablets a week, *some of which were ineffective*. He entered the hospital after a prolonged bout of pain that occurred during the night.

Physical examination revealed a normally built man five feet seven inches tall and weighing 155 pounds who had no signs of congestive heart failure at rest. His blood pressure varied from 160/100 to 150/100 mm. Hg in each arm. There was a bilateral arcus senilis. There was a slight precordial and apical systolic lift and a third heart sound.

The electrocardiogram (ECG) showed minimal prolongation of the duration of the QRS complexes, occasional premature ventricular beats, and QS complexes *in the right precordial lead, indicative* of an old anteroseptal myocardial infarction.

The laboratory studies including a blood count, urinalysis, cholesterol, total protein with albumin, total bilirubin, calcium, uric acid, creatinine, phosphorus, alkaline phosphatase, lactic dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), creatine phosphokinase activity (CPK), glucose, blood urea nitrogen (BUN), Na, K, Cl, and CO_2 were all within normal limits. The chest x-ray showed a normal cardiovascular silhouette and clear lung fields. Right atrial pacing, the technique of which is described elsewhere,[1] cardiac catheterization, and selective coronary arteriography were carried out on October 10, 1969. Pulsus alternans occurred just before the onset of pain. Pain occurred repeatedly at a time pressure index of 3,900. Cardiac catheterization revealed normal pressures with a left ventricular end-diastolic pressure (LVEDP) of 10 mm. Hg. The left ventricular cavity was minimally enlarged but its contractility was normal. The left coronary artery showed diffuse atherosclerotic changes with a 70 per cent narrowing 2 cm. *from its origin. The left circumflex artery* was completely occluded just beyond its origin. The right coronary artery showed severe atherosclerotic changes with more than 60 per cent narrowing in its first 4 cm.

The patient was discharged on a medical regimen that included digoxin, furosemide, and propranolol. This treatment was unsuccessful. He developed severe chest pain while filling the tires of his automobile with air and was readmitted for surgery to revascularize his heart.

Surgery was performed on October 30, 1969. This consisted of an aortic-right coronary bypass using a

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saphenous vein graft and a Vineberg procedure using the left internal mammary for implantation into the anterolateral portion of the left ventricle On November 21 1969 aortography revealed a patent bypass

Within a month after d s harge from the hospital the patient experienced difficulty in catching his breath wh le climbing steps and walking a short distance to his parking lot. Over the following six months dyspnea increased so that it occurred after walking as little as one half city block and also awakened him from sleep At no time did he have pain or require the use of nitroglycerin.

The patient was readmitted into the hospital in July 1970 for cardiac re evaluation. Although the patient had developed pain previously when his atrial rate had been increased to 125 beats per min ute pain did not occur even though the atrial rate was raised to 130 beats per m nute It was not possi ble to raise the atrial rate higher because of the production at this rate of a second-d gree block

Cardiac catheterization revealed that the left ventricle had increased markedly in size and ex hibited extremely poor traction. Nevertheless both the bypass and the internal mammary implant were widely patent. The LVEDP had increased to 35 mm. Hg the right ventricular pressure to 67/13 mm Hg and the pulmonary artery pressure to 67/30 mm. Hg The right atrial A wave was 13 mm Hg and the Y wave was 12 mm Hg The anterior and apical portions of the left ventricle were virtually motionles

The pat ent was rejected for reoperation by the cardiac surgeon.

Case 2 P W a 52 year old white man was first een at Temple University Health Sciences Center on June 7 1971 He gave a history of having suffered a myocardial infarction in 1963 He had recovered completely and was well until 1970 when he ex perienced a burning sensation retrosternally not d ssimilar to the initial sensation that ushered in his myocardial *infarction in 1963* Soon thereafter he developed pain after walking two city blocks

Physical examination revealed a slightly built man five feet six inches tall and weighing 140 pound with no signs of congestive heart failure at rest His blood pressure var ed from 140/100 to 120/90 in each arm There was a minimal systolic lift from the third left intercostal space to the apical thrust that was just outside the mid clavicular l ne in the fifth intercostal space There was an audible th rd heart sound

The ECG showed non specif c ST and T abnor mal ties and QS complexes in the right precordial leads ind cative of an old anteroseptal myocardial infarction

The blood cholesterol was 324 mg per cent. Other laboratory stud es incl ding a blood count urinalys s blood sugar urea nitrog n phosphorus calcium phosphatase electrolytes and enzymes were all normal

Cardiac catheterization revealed a min mally en larged left ventricular cavity and a small akinetic apical region *with* an irregular contour suggest ng the prese ce of a thrombus. Coronary arteriography showed almost complete obstruction of the proximal portion of the anterior descending artery 1½ cm. from its origin with delay in di tal perfusion. The right coronary artery showed a 50 per cent fu form segmental narrowing in its proximal portion extend ing over several centimeters.

The patient was discharged on a medical trial of propranolol digoxin furosemid nitroglycerin and Librium. This treatment was ineffective

His pain gradually increased so that he became totally incapacitated He could not work and could not walk more than half a city block without de veloping severe pain in his chest

On August 12 1971 he underwent cardiac surgery A resect on of the apical portion of the left ventricle that contained a thrombus was performed together with an aortic ri ht coronary saphenous vein graft bypass and a left si led Vineberg pro- cedure He developed three ep sodes of ventricular fibrillation after operation each of which was im mediately converted electrically to sinus rhythm. He then became asymptomatic and was discharged from the hospital on Persantin aspirin digoxin and Valium

Following di charge from the hospital the patient became depressed because he felt extremely tired was aware that his heart was beating rapidly and that it was difficult and made him breathless to raise an object weighing as little as 15 pounds It was for this reason that he was unable to return to work However all during this time he was taking no nitro- glycerin tablets and had had no chest pain

Because of his extremely poor effort tolerance shortness of breath and a heart rate that was con stantly above 100 beats per minute even at rest he re-entered the hospital on October 14 1971 for recatheterization

The laboratory studies including a blood count urinalysis SMA6 and SMA12 were again within *normal limits* The ventriculogram showed that the entire apical region was akinetic. There was appreciable mitral insufficiency The grafts were patent.

Although visualization of the vessels was not ideal one gained the impression that there was no significant change in their morphology compared to the previous study

All intracardiac pressures were above normal The LVEDP had increased to 23 mm Hg His sleeping heart rate was 100 beats per minute

Case 3 R. K. a 67 year-old white man was ad mitted to Temple University Hospital on January 26 1969 because of increasing chest pain. He had a history of cardiac pain for over four years at first promptly relieved by nitroglycerin At the beginning the pain occurred only in the morning when he left his house for work and was quickly relieved by nitroglycerin. During the past *two* years cardiac pain had recurred frequently during the day and for the past few months had awakened him one to three times a night from sleep He had no shortness of breath and no fatigue

Phy cal examination reveal d a normally built man five feet eight inches tall and weighing 167 *pounds* who showed no signs of congestive heart failure His blood pressure was 160/90 in each arm There was a Grade I/VI systol c early ejection murmur at the apex occupying the first third of systole A fourth heart sound was audible

Laboratory studies including a blood count urinalysis cholesterol total protein with albumin total bilirubin calcium uric acid creatinine phosphorus alkaline phosphatase LDH SGOT CPK glucose BUN Na K Cl and CO_2 were all normal

The ECG showed non-specific ST segment and T wave abnormalities in the left precordial lead Cardiac catheterization revealed that the left ventricle was minimally enlarged but contracted normally

Coronary arteriography gave evidence of occlusive disease of the three major coronary arteries The left circumflex artery was completely obstructed about 2.5 cm distal to its origin and multiple marginal branches were seen bypassing the obstruction and filling the posterior part of the left ventricle There was more than 50 per cent narrowing of the anterior descending artery with relatively large distal branches The right coronary artery was also obstructed about 2 to 3 cm distal to its origin and again multiple tortuous vessels were seen representing collateral circulation The intracardiac pressures were all normal including the LVEDP which was 8 mm Hg He was discharged on January 31 1969 and readmitted the following month when a Vineberg operation was performed

The patient developed a postoperative myocardial infarction as indicated by the appearance of significant Q waves in Leads II aVF and III and coving of the ST segments and negative T waves in the lead Nonetheless he was free of pain except for the usual incisural complaints He remained completely free of pain until March 1971 He did develop however shortness of breath and occasional edema of the ankles which required an intensification of his diuretic therapy and increased restriction of all intake of salt During this time he also developed an audible third and fourth heart sound

In March 1971 pain reappeared Because the patient was convinced that his cardiac operation had been successful he requested recatheterization as a prelude to a second cardiac operation

Cardiac catheterization was carried out on April 19 1971 The left ventricle had enlarged considerably There was a moderate sized left ventricular aneurysm at the apex There were also other regions of dyskinesia throughout the entire left ventricle which contracted poorly and emptied extremely slowly

Coronary arteriography showed occlusion of all three major coronary vessel The left anterior descending coronary artery was occluded 1 to 2 cm distal to its origin The left circumflex artery was occluded 4 cm distal to its origin The right coronary artery was occluded for the first 8 cm There were abundant collaterals from the proximal occluded vessels to the distal vessels There was however no crossover of collaterals from the right coronary artery to the left coronary artery or vice versa

An ascending aortic injection was made to visualize the internal mammary arteries Both were well seen and patent

All intracardiac pressures were elevated The LVEDP was 28 mm Hg the right ventricular pressure 44/7 mm Hg and the pulmonary artery pressure was 47/18 mm Hg

The patient was rejected by the surgeon for operation and died in June 1971

Discussion

These case reports illustrate that cardiac deterioration can replace cardiac pain after present day operation performed in an attempt to revascularize the heart We have made similar observations after other operative procedures used in an attempt to increase the arterial blood supply to the heart Indeed it has been noted for years that there frequently appears to be an antagonism between cardiac pain and congestive heart failure The mechanism underlying the paradox of cardiac deterioration replacing cardiac pain (particularly after saphenous vein bypass, an apparently logical method of revascularizing the heart), is not clear

In 1809, Burns formulated the concept that cardiac pain is due to diminished blood flow to the myocardium and this concept is now universally accepted However since the introduction of present day surgical procedures to revascularize a heart, almost no studies have been aimed at determining just how diminished blood flow to the heart produces pain This void is in sharp contrast to the many studies devoted to this subject in the first half of this century which appeared after the classic studies by Lewis[2] Furthermore little notice is paid today to the fact that diminished blood flow to the heart is often present without cardiac pain and that cardiac pain is a sensation of conscious man

Pain is a reaction and interpretation of conscious man to stimuli which create impulses that are transmitted by nerve endings and nerve fibers to the brain where they are recognized as pain by conscious man The specific reaction and interpretation of these impulses depend upon the character the number and the intensity of the stimuli the reaction of the nerve endings and nerve fibers that react to the stimuli and the reaction of the brain itself The efferent pathway is important but does not have to be intact as evidenced by pain of a phantom limb

Pain can be relieved by (1) changing the reaction of the brain—e g through sedation tranquilizer or frontal lobotomy, (2) changing the reactivity of nerves that

transmit the pain sensation—e g by Novocaine or cutting the nerve (3) changing the intensity character and number of stimuli—e g rest lowering blood pressure decreasing heart rate thyroidectomy beta blockers or carotid sinus stimulation and (4) removing the stimulus that activates the pain fibers Hopefully this is what in some way the bypass operation and other operations used to revascularize the heart will accomplish

In 1920 Jonesco[4] divided the first four or five left posterior thoracic roots of the sympathetic chain This procedure gave considerable relief of cardiac pain referred to the left arm and pectoral muscles Our group performed eight such operations in the early 1930 s This procedure was universally abandoned because pain frequently appeared on the opposite side and in the neck and jaw and occasionally a Brown Séquard syndrome was produced Most importantly life was not appreciably prolonged by the operation Although Gross and associates[5] introduced experimental methods to increase the blood supply to the heart and Beck[6] was the pioneer in attempts to revascularize the human heart in the 1930 s and 1940 s from 1930 to 1950 the greatest amount of surgical work to relieve cardiac pain was sensory denervation

Beck[6] was the first to attempt to revascularize the human heart in an attempt to relieve cardiac pain and to improve myocardial function It is noteworthy that Feil[7] a pre eminent cardiologist and an experimental and clinical investigator of cardiovascular disorders assessed Beck s results and came to the conclusion that 69 per cent of the patients who survived Beck s operations were improved This percentage remained constant no matter what procedure was used by each subsequent surgeon including the procedure of throwing talc into the pericardial sac[8]

Skeptics thought that the relief of cardiac pain by these surgical procedures was psychologic (i e a change in reaction of the brain) and surgical enthusiasts thought that the relief of cardiac pain was due to an increase in blood flow to the myocardium No effort was made to determine how the presumed increase in blood flow relieved pain This was understandable because there were no procedures at that time to measure coronary flow myocardial energetics and cardiac metabolism in the human heart

Lewis[3] was the first to attempt to elucidate the mechanisms of skeletal and by analogy cardiac pain He came to the conclusion that pain was initiated by a catabolic substance P which reached a concentration and duration of concentration sufficient to activate the surrounding nerve fibers that transmit the pain sensation to the brain The concentration high enough to provoke pain was more quickly reached the greater the retarded flow across an obstruction in a vessel Cardiac pain therefore could be relieved in at least two ways (1) remove the vascular obstruction and thereby decrease the concentration and duration of concentration of P below the threshold necessary to produce pain and (2) destroy or change the reactivity of the nerve endings and fibers surrounding the obstructed vessel which cause the sensation of pain

Sutton and Lueth[9] used the second method to abolish pain in the experimental animal They wrote it has been definitely *found that temporary* partial or complete interference with blood flow in a coronary artery or vein invariably produces pain The nerve fibers responsible for conducting the pain sensations from the heart are those fibers in the adventitia of the blood vessels or adjacent tissues This is indicated by the absence of pain after painting the stripped arterial wall with 80 per cent alcohol

In 1946 Fauteux[10] applied this method successfully in man Nonetheless all methods that involve deliberate sensory denervation of the heart were discarded because (1) it was thought at that time dangerous to abolish a signal that warned the patient not to overtax his heart and (2) these procedures did nothing to improve the blood supply to the heart Indeed it was postulated that relief of cardiac pain after myocardial infarction was due to necrosis of the pericoronary nervous plexus adjacent to the myocardium Such relief of pain could not be regarded as indicative of improvement of blood supply to the heart In addition technical advances had made it safer to attempt revascularization

of the heart Finally the introduction of catheterization of the coronary arteries by Sones and Shirey[11] made it possible to identify and to attempt to bypass obstructions of the coronary arteries

There appear to be at least two organic causes for relief of pain after saphenous vein bypass and other types of operations to revascularize the heart (1) Decrease in concentration and duration of concentration of Lewis s P substance consequent to an improvement in coronary flow, and (2) destruction or change in reactivity of the pericoronary nerve plexus Either cause can occur without the other Thus, cardiac deterioration could replace cardiac pain if the surgical operation damaged the myocardium and at the same time destroyed the pericoronary nerve plexus

There are of course other possible causes for cardiac deterioration replacing cardiac pain For instance, it is possible that pain results when an excessive and rapid muscular stretch impinges on the nerve endings Cardiac deterioration could decrease a localized excessive and rapid muscular stretch and thereby abolish the stimulus for the production of pain Thus, in the 1950 s when I was using norepinephrine in an attempt to identify the significance of cardiac murmurs,[12] cardiac pain could be produced by a sudden elevation of systemic arterial pressure but was absent at higher levels of blood pressure provided the rise in blood pressure was slow It is also possible that cardiac mitochondria and other adaptive mechanisms in the heart can cope with the effects produced by slow but not by rapid stretch and increase in pressure

In any case relief of cardiac pain by medical or surgical means, although an important function of the physician is not tantamount to improvement of cardiac function and does not exclude deterioration in the function of the heart

Conclusion

Three case histories are given to illustrate that relief of cardiac pain after cardiac surgery performed in an attempt to revascularize the heart does not exclude deterioration of the heart after surgery

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Analysis of intracavitary electrocardiograms through a saline bridge in the diagnosis of cardiac arrhythmias

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Analysis of intracavitary electrocardiographic morphology through an electrode introduced into the right atrium has been reported to be of value in the diagnosis of certain cardiac arrhythmias[1-6] and of congenital heart defects.[7,8] This procedure, however, requires the use of a special wire catheter; it is time consuming in emergency situations and it discards a vein which could be used to obtain other parameters, such as central venous pressure (CVP), and therefore limits the information to the electrocardiogram (ECG) alone.

We have used the conventional catheter for the measurement of CVP in critically ill patients to obtain, in addition, intracavitary ECG's (IECG) by simply filling the catheter with a saline solution, transforming it into a good electrical conductor.[9]

The procedure is simple; it can be done at the bedside; it does not require any special equipment or training; and it facilitates the identification of atrial electrical activity.

This study presents evidence which suggests the usefulness of this method in the differential diagnosis of certain cardiac arrhythmias in critically ill patients.

Materials and methods

The subjects of this study were 120 patients admitted to the general intensive care unit from January to December, 1970.

Of these patients, 35 were admitted with the diagnosis of acute myocardial infarction, 45 because of acute respiratory failure, and 40 because of cardiac arrhythmias.

In all patients a Teflon catheter was introduced into an antecubital vein or by supraclavicular subclavian puncture and passed to the superior vena cava. The external tip of the catheter was connected to a three-way stopcock. An alligator clip was attached to one of the outlets of the stopcock and connected to the exploring electrode of the electrocardiograph. The other outlet was connected to a syringe containing 10 per cent sodium bicarbonate

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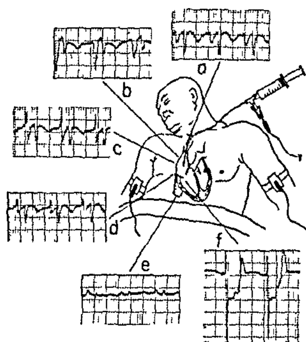


Fig. 1. ECG patterns obtained by means of intracavitary catheterization.

The catheter was then filled with the bicarbonate solution and the stopcock closed by turning the valve to an intermediate position. At this time the solution becomes an electrical conductor and an IECG can be obtained.

The position of the tip of the catheter was recognized by interpretation of the intracavitary electrocardiographic morphology, according to the method described by Kimball and Killip.[10,11]

This procedure was performed routinely in all patients with the above mentioned diagnoses. The catheter could in addition be used for the assessment of CVP—a valuable item of information in the care of critically ill patients.

Results and comments

Interpretation of intracavitary electrocardiographic morphology permitted us to know the exact position of the tip of the catheter in the cardiac chambers. Fig. 1 shows the electrocardiographic patterns obtained with this method, according to the position of the tip of the catheter.

In the superior vena cava it revealed a negative atrial complex smaller than the ventricular complex. In the right atrium the ECG showed a large atrial complex, larger than the ventricular one.

In the mid right atrium a high voltage isodiphasic atrial complex and small negative ventricular complex were seen. Occasionally the catheter passed to the right ventricle and the IECG obtained showed P waves similar to those observed using standard leads and high voltage ventricular complexes. We have also observed ECG's of the coronary sinus.[1] This may be of interest since the administration of large amounts of fluids with the catheter in that location could produce hemodynamic changes in the coronary vessels.

Comparison of the ECG's obtained by conventional methods and those obtained by using a catheter with a saline bridge may be seen in Fig. 2. The four upper tracings, obtained by conventional methods, show normal sinus rhythm. The two lower tracings were obtained by the saline bridge method described herein with the tip of the catheter located in the upper right atrium. A prominent negative P wave and a QS ventricular complex are shown. The tracings obtained have a stable base line, are of neat quality, and show no artifacts.

Examples of patients in whom this method was of value for the diagnosis of certain arrhythmias may be seen in Figs. 3 to 6.

In Fig. 3 Leads II and V_1 in the upper tracings show a ventricular rate of 150 per minute, regular R-R intervals, and QS complexes of normal amplitude and duration. It is difficult to identify P waves. The middle tracing obtained by use of an intracavitary catheter with a saline bridge shows that each ventricular complex is preceded by two isodiphasic P waves with an atrial rate of 300 per minute, thus clarifying the diagnosis of 2:1 atrial flutter. The lower tracings show the pattern obtained after DC shock—on the left side standard Lead II, on the right the IECG with the tip of the catheter located in the upper right atrium.

Fig. 4 shows two upper tracings with aberrant ventricular complexes at a rate of 170 per minute, irregular R-R intervals, and absent P waves. The two diagnostic possibilities are (1) ventricular tachycardia and (2) atrial fibrillation with abnormal conduction. The third strip is an intracavitary ECG showing absent P waves and

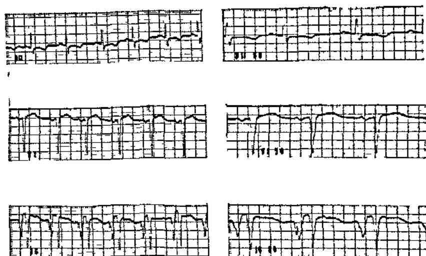


Fig 2 Comparison of ECG s obtained by conventional method and those obtained by using a catheter with a saline bridge

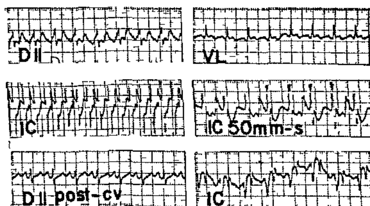


Fig 3 Comparison of ECG s obtained by various methods (see text)

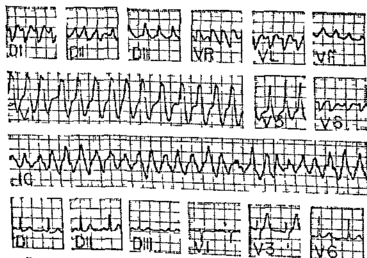


Fig 4 Comparison of ECG s obtained by various method (see text)

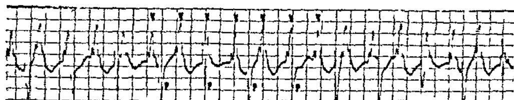


Fig 5 IECG of a patient with ventricular tachycardia

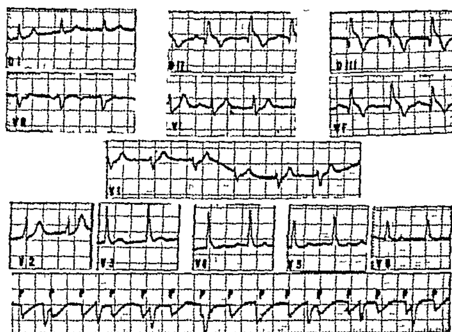


Fig 6 Standard ECG of a patient with inferior myocardial infarction complete A V block and cardiogenic shock

abnormal and irregular ventricular complexes confirming the diagnosis of atrial fibrillation with abnormal conduction The lower strip shows a standard ECG after cardioversion

Fig 5 shows an IECG of a patient with ventricular tachycardia Atrial complexes are negative at the rate of 100 per minute Ventricular complexes are aberrant with independent rhythm at a rate of 155 per minute

Fig 6 shows the standard ECG of a patient with inferior myocardial infarction complete A V block and cardiogenic shock receiving isoproterenol intravenously at the rate of 4 μg per minute The atrial rate is 175 and the ventricular rate is 115 per minute but it is rather difficult to distinguish the atrial rhythm The IECG permits an easy appreciation of the P waves confirming the diagnosis of complete A V block with high ventricular frequency

Summary and conclusions

Analysis of intracavitary electrocardiographic morphology is useful for the diagnosis of certain cardiac arrhythmias in critically ill patients The procedure presented herein using a conventional catheter for CVP measurements and a saline bridge for electrocardiography is in our experience a simple technique which can be performed at the bedside and does not require special training or equipment It can be done rapidly in emergency situations or routinely on admission of the patient with the advantage that the catheter can be left in place for many days thus allowing the physician to repeat IECG and/or CVP measurements as often as needed In addition, the tracings obtained by this method have a stable base line are of good quality, and show no artifacts

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Response of Class IV patients to alpha blockade prior to open-heart surgery

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The largest number of deaths from intracardiac surgery and valve replacement occurs in the clinically identifiable poor risk or functional Class IV patient.[1-4] Low cardiac output or "pump failure" at the termination of perfusion, or in the immediate postoperative period, is the single greatest cause of death in this group.[2,5] Additional risk factors are pulmonary hypertension, advanced age, marked cardiomegaly,[1,4,5] a reduced cardiac index, multivalvular disease, and cardiac arrhythmias.[5]

Phenoxybenzamine, a potent alpha blocker with prolonged action, has been found useful in the treatment of hemorrhagic, traumatic, and septic shock.[6-8] However, it is most effective in increasing survival when administered prior to the induction of experimental shock.[6] The manifestations of clinical shock are similar to the postoperative low cardiac output syndrome.[8] These factors led us to use alpha blockade in functional Class IV patients prior to the induction of anesthesia for open heart surgery and valve replacement.

Patient selection and methods

The seven patients selected were bedridden with end stage disease and functional Class IV by New York Heart Association criteria (Table I). Their ages ranged from 39 to 65 years, with an average age of 55.6 years. The group consisted of five women and two men with multivalvular disease and massive cardiomegaly. Four patients had primarily mitral valve and three aortic valve lesions. Established auricular fibrillation was present in six patients; the seventh had complete heart block.

Preliminary right and retrograde left heart catheterization and cineangiograms were accomplished in six patients, one patient (A. S.) was too ill for this procedure. Cardiac outputs were markedly depressed, as indicated by an average cardiac index of 1.4 L. per minute per square meter and arteriovenous (A-V) oxygen difference of 9.1 volumes per cent. Pulmonary hypertension was present; the average pulmonary artery systolic/diastolic pressure was 79/40 mm. Hg with a pulmonary artery mean of 51.5 mm. Hg. The pulmo-

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Table I. Preliminary clinical and hemodynamic data

Patient	Age	Preop Dx	Rhythm	Functional class	Pressures (mm Hg)					A V O_2 (vol %)	CI (L/min/M^2)	Dynes sec-cm^{-5}		
					PA		RVED	PW M	LVED			PVR	TPR	SVR
					S/D	M								
B C	39	AS AI	AF	IV	75/43	47	18	27	28	11 4	1 1	865	2 032	4 237
L D	59	MS MI MS TI	AF	IV	55/30	43	1	28	5	10 3	1 2	679	1 81	3 995
A B	6	MS MI AS AI	Complete heart block	IV	56 28	37	6	3	10	8 9	1 4	459	1 533	2 674
S G	59	MS MI TI AI	AF	IV	79/43	5	14	23	16	8 5	1 1	958	1 491	411
J G	65	AS AI MI	AF	IV	110/55	72	11	38	33	8 9	1 8	961	035	3 816
G H	59	AI AS MI TI	AF	IV	104/38	58	15	23	1	6 3	1 8	848	1 406	2 667
A S	46	MS PI TI	AF	IV	—	—	—	—	—	—	—	—	—	—
Average	55 6				79/40	51 5	10 8	25 5	18 8	9 1	1 4	800	1 441	3 500

Abbreviations Dx = diagnosis AS = aortic stenosis AI = aortic insufficiency MS = mitral stenosis MI = mitral insufficiency TI = tricuspid insufficiency PI = Pulmonary insufficiency AF = auricular fibrillation PA = pulmonary artery S/D = systolic/diastolic M = mean RVED = right ventricular end-diastolic pressure PW = Pulmonary wedge LVED = left ventricular end diastolic pressure A V O_2 = arteriovenous oxygen difference CI = cardiac index PVR = pulmonary vascular resistance TPR = total pulmonary resistance SVR = systemic vascular resistance

nary wedge mean was 28 5 mm Hg The calculated average pulmonary vascular resistance total pulmonary resistance and systemic vascular resistance were 8 12 and 3 times normal respectively

The patients breathing room air were taken to the recovery room area prior to anesthesia for open heart surgery Their critical condition permitted us to obtain only readily accessible physiologic measurements The patients urinary bladders were emptied by catheters which were left in place Whole blood was present for added volume as required The pulse rate and heart rhythm were monitored by Lead II of the electrocardiogram (ECG) on a display screen The blood pressure was measured indirectly with a sphygmomanometer left in place A central venous catheter was inserted percutaneously into an antecubital vein and advanced centrally to the superior vena cava Catheter position was verified radiographically Central venous pressure was measured by a water manometer with zero level being the mid thorax Heparinized syringes after flushing were used to obtain venous blood from the central venous pressure catheter and arterial blood from percutaneous punctures of the brachial artery The blood samples were analyzed for P_{O_2} P_{CO_2} and pH by the Astrup method[9] Partial gas pressures were corrected for pH and temperature using a Siggard Andersen curve nomogram[10] and corresponding oxygen saturation was obtained from a hemoglobin dissociation curve The A V oxygen difference was computed by converting oxygen saturation to volumes per cent (Hgb $\times$ 1 34 $\times$ O_2 saturation = volumes per cent) In the critically ill patient a fall in central venous oxygen saturation has been accompanied by an increase in A V oxygen difference and a rise in central venous oxygen saturation by a narrowing of A V difference and improvement in cardiac output[11] The changes in central venous oxygen saturation have greater significance than the absolute value[12]

In the last three consecutive patients cardiac outputs were estimated by the dye dilution technique using indocyanine green

dye A known amount of dye was injected rapidly through the central venous catheter Blood was drawn from the femoral artery with a Gulford constant withdrawal pump and dye concentration was measured with a Beckman model 350 127 densitometer and integrator Values for cardiac output represent an average of two successful determinations varying by less than ten per cent Although the accuracy of the dye dilution technique in estimating cardiac output in the low cardiac output states has been questioned, it has been accepted as being reliable for comparison of outputs in individual patients over a short period of time as in our study [13,14]

Following control studies, phenoxybenzamine was administered intravenously in a dose of 1 mg per kilogram in 250 c c of glucose in water over a 90 minute period At 5 minute intervals the central venous pressure, blood pressure and fluid intake and output were monitored With the completion of the phenoxybenzamine administration, arterial and venous oxygen saturation studies were repeated, and in the last three consecutive patients cardiac outputs were again determined

The patients were then taken to the operating room where they were given anesthesia, were intubated, and underwent open heart surgery The operative period was divided into the preperfusion, perfusion and postperfusion periods During the operative period there was constant observation of the blood pressure, central venous pressure, fluid intake and output, pulse rate, and heart rhythm Serial determinations of arterial and central venous blood Po_2, Pco_2 and pH were analyzed by the Astrup method With the completion of surgery the patients were returned to the recovery room During the ensuing 24 hour period with the prolonged alpha blocking effects of phenoxybenzamine still effective, continued serial recordings were made of the same parameters

Results

During the 90 minute preanesthesia infusion of phenoxybenzamine the maximum mean fall in central venous pressure was 72 mm H_2O (Fig 1) The total mean fall was 54 mm H_2O following the addition of volume (blood) to five patients The patients with initial marked elevations had the largest fall Those with normal or low central venous pressure required volume to maintain control levels and prevent further declines The percentage fall in blood pressure was not as marked and lagged temporally behind the central venous pressure The mean maximum fall in systolic and diastolic blood pressure was 20 and 13 mm Hg, respectively The mean urinary output was 1 2 ml per minute

When the phenoxybenzamine infusion was completed determination of the mean central venous oxygen saturation revealed a rise from a control level of 46 2 per cent to 58 2 per cent (25 9 per cent) In one patient (J G) the central venous oxygen saturation fell from 72 5 to 63 5 per cent The arterial oxygen saturation had a mean fall from 93 8 to 88 6 per cent (5 5 per cent) The A V oxygen difference mean narrowed from 9 2 to 5 5 vol per cent (40 2 per cent) The last three consecutive patients who had cardiac output studies showed a rise from a mean control level of 3 to 4 3 L per minute (43 3 per cent) The calculated mean cardiac index rose from 1 9 to 2 6 L per minute per square meter (36 8 per cent) (Fig 1)

The total mean surgical time from the induction of anesthesia to skin closure was 300 minutes (Fig 2) The preperfusion period averaged 90 minutes, the perfusion time 120 minutes and the postperfusion period 90 minutes A mean maximum perfusion rate of 90 4 ml per kilogram per minute (3 1 L per minute per square meter) was achieved The mean initial and final surgical central venous pressure and blood pressures were 163 and 168 mm H_2O and 114/76 and 101/74 mm Hg, respectively The pH mean was 7 35 just prior to perfusion and 7 54 at the end of the perfusion In weaning patients from the pump added volume was necessary and well tolerated Inotropic drugs i e, isoproterenol (two patients) norepinephrine (two patients), and ouabain (one patient) were effective when required

Immediately postoperatively the patients were warm their pulses were all present and the urinary output was substantial The patients were all intubated and on assisted ventilation with 60 per cent oxygen during this period They responded well to the administration of inotropic

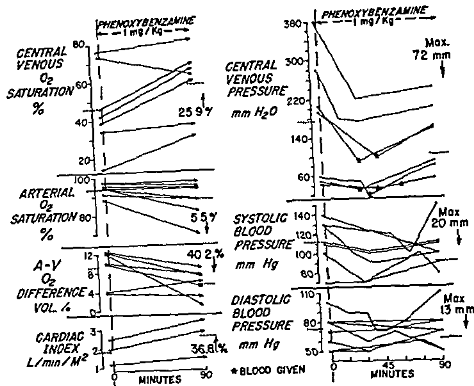


Fig *1* Phenoxyb nzamine infu ion prior to anesthesia The data on the left were obtained prior to and following the completion of drug admini tration The data on the right were recorded during phenoxybenzamine infusion The horizontal dotted line i the mean value indicates the addition of volume

drugs when required During the first 24 hours postoperatively mean intake was 4 683 ml (195 ml per hour) fluid output was 3 130 ml (130 ml per hour) of which 1 869 ml was in the form of urine (78 ml per hour) and the remainder as drainage The mean initial and final 24 hour central venous pressures were 146 and 159 mm H_2O blood pressures 110/76 and 101/63 mm Hg and pH 7 39 and 7 45 respectively (Fig 2)

A total of five mitral and four aortic prosthetic valves were inserted with three patients having two valve replacements One patient (A S) had a bilateral pulmonary artery embolectomy left atrial thrombectomy and mitral commissurotomy One patient (J G) had an aortic valve replacement and mitral commissurotomy All seven patients survived surgery and the immediate postoperative period One patient (S G) died two weeks postoperatively from recurrent hemorrhage The other six patients at hospital discharge were ambulatory and able to care for themselves

Discussion

Patients who have the low cardiac output syndrome following cardiopulmonary bypass exhibit the hallmark of clinical shock They are cool and cyanotic and have increased peripheral resistance reflected by a narrow pulse pressure Lillehei and associates[3] have noted the absence of postoperative vasoconstriction with the prior use of phenoxybenzamine The frequent elevation of central venous pressure in these patients precludes volume loading despite the common occurrence of major volume deficits The onset of oliguria or anuria often precedes total renal failure

When cardiopulmonary bypass is prolonged beyond one hour poor tissue perfusion due to capillary constriction results in acidosis and is accompanied by a 5 to 15 fold increase in plasma catecholamines[15] Phenoxybenzamine does not prevent this rise in catecholamines but may act upon alpha adrenergic receptor sites decreasing or abolishing their receptivity to sympathomimetic stimuli[8] This may have allowed

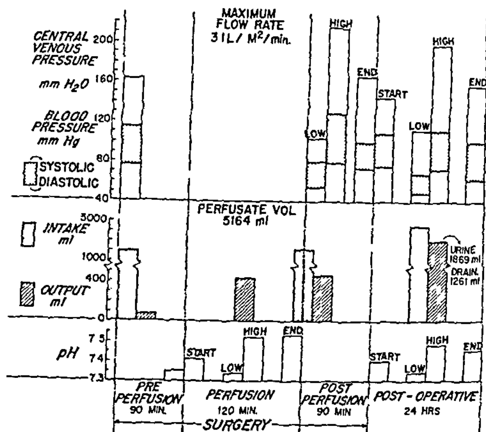


Fig 2 Data obtained during surgery and in the immediate 24 hour postoperative period in the phenoxybenzamine pretreated patients

a more complete perfusion with the high flow rates we achieved and enabled complete volume loading at 'pump weaning' and in the postperfusion period The effectiveness of inotropic drugs is not altered in the presence of alpha blockade [16] and we used them effectively in "pump weaning" and during the 24 hour postoperative period Phenoxybenzamine may have direct inotropic action on the myocardium and metabolic liver effects as well as its alpha blocking action [6,16,17] The increase it produces in cardiac output may be related to carotid and aortic baroreceptor reflex mechanisms [18]

Our seven functional Class IV patients given phenoxybenzamine prior to anesthesia had a rise in central venous oxygen saturation and a narrowing of A V oxygen difference and when measured in three patients an increase in cardiac output This occurred despite fixed valve obstruction or insufficiency These results may reflect relief of postcapillary pulmonary vasoconstriction with increased venous return to the left heart the shifting of volume from the engorged pulmonary bed to the systemic vascular bed a fall in peripheral resistance with a resultant decrease in the after load of the heart, and increased capillary perfusion with improved O_2 CO_2 transport in tissues [18,19,20] Increased volume was required in five of our patients to fill the dilated venous capacitance bed and maintain ventricular filling pressure [21] The failure of the central venous oxygen saturation to rise in one patient (J G) may have resulted from inadequate volume replacement during phenoxybenzamine infusion as shown by her low central venous pressure The fall in arterial oxygen saturation is probably secondary to temporary shunts and ventilation perfusion defects due to pooling of blood in the dilated vascular bed [20] The increase of cardiac output during the control period of the three patients, compared to their preliminary catheterization, demonstrates the benefits of prolonged intensive preparation prior to surgery with bedrest digitalis and diuretic therapy [2] This resulted in the loss of 55 pounds of fluid in one of our patients (G H)

The prolonged action of phenoxybenza

mine makes it effective during the entire surgical procedure and the critical first 24 hour postoperative period Cardiac output is at its lowest level three to four hours following the completion of intracardiac surgery[11] Renal function despite high flow rates is often markedly impaired during extracorporeal circulation and in the immediate postoperative period[2,3] Phenoxybenzamine effectively increases renal blood flow through inhibition of efferent arteriolar vasoconstriction in the presence of increased catecholamines[24] The large volume intake our patients tolerated during their first 24 hour postoperative period with a stable central venous pressure blood pressure pH and good urinary output is a measure of the effectiveness of pretreatment with phenoxybenzamine in preventing the low cardiac output syndrome and all of its sequelae

Summary

Seven bedridden functional Class IV patients were given phenoxybenzamine intravenously (1 mg per kilogram) over a 90 minute period prior to anesthesia for intracardiac surgery and valve replacement

Their mean central venous pressure fell maximally by 72 mm H O Mean maximum fall in systolic and diastolic arterial blood pressure was 20 and 13 mm Hg respectively Volume was required in five patients to maintain the central venous pressure and blood pressure The central venous oxygen saturation rose by 25 9 per cent The A V oxygen difference narrowed by 40 2 per cent The cardiac output and cardiac index rose 43 3 and 36 8 per cent respectively when measured in the last three consecutive patients

High flow rates were achieved in perfusing the dilated vascular bed Pump weaning required volume and inotropic drugs Postoperative peripheral vasoconstriction was absent volume loading was well tolerated urinary output was large and inotropic drugs were effective The central venous pressure blood pressure and pH were stable All patients survived in this anticipated high mortality group with one late death The low cardiac output syndrome did not occur

Alpha blockade may be a significant adjunct in the preoperative preparation of the functional Class IV patient prior to open heart surgery and valve replacement

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The scoliosis of congenital heart disease

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The incidence of scoliosis is increased in patients with congenital heart disease (CHD)[4,8,10,15] This scoliosis may impose an added respiratory burden on the individual whose cardiorespiratory function is already impaired by heart disease Knowledge of the natural history of the scoliosis will help in improving treatment for these patients

The age when the scoliosis begins and its pattern of development have not been well documented The present study was designed to evaluate these variables and to correlate age of onset direction of curvature and severity of the curve with such parameters as the type of CHD the side of the aortic arch and the effect of surgery

Method

For this study 129 patients were chosen at random from the Adolescent Cardiac Clinic of the Johns Hopkins Hospital In this clinic patients with CHD continue to be followed after adolescence Three groups of patients were excluded from the study (1) patients with trisomies (2) patients with cyanotic forms of CHD and a hematocrit below 5? per cent and (3) patients with tetralogy of Fallot and total corrective surgery more than six months before the study

An erect frontal radiograph of the thoracic and lumbar spine and a radiograph of the right hand were obtained in each patient Of these patients 78 per cent had had serial chest radiographs for at least five years previously and 50 per cent for at least twelve years These were reviewed and compared with the current spine radiographs with reference to the onset and course of the scoliosis Skeletal maturation was determined by reference to a standard atlas[6]

The scoliotic curve was determined by the Cobb method[1] and graded as mild (curve < 10°) moderate (curve 10° to 30°) or severe (curve > 30°) Spinal curvatures greater than 10° were readily measured while curvatures of less than 10° could not be measured accurately A patient was considered to have mild scoliosis when the spine roentgenogram obtained for this study and three previous chest roentgenograms consistently revealed the presence of a spinal curvature Poorly positioned chest radiographs were excluded Age of onset of the scoliosis and the time of rapid progression were noted

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Table I Incidence of scoliosis in 121 patients with CHD

	No	Normal (%)	Mild* (%)	Moderate† (%)	Severe‡ (%)
Acyanotic patients	65	76	15	9	0
Male	42	81	12	7	0
Female	23	65	22	13	0
Cyanotic patients	56	34	36	23	7
Male	36	42	25	25	8
Female	20	20	55	20	5
Total	121	56	25	16	3

*Mild = curve < 10
†Moderate = curve 10 to 30
‡Severe = curve > 30

Table II Patients with severe scoliosis (>30°)

No	Curvature	Sex	Age (yr)	Cyanotic
1	76	F	23	Yes
2	55	M	13	Yes
3*	54	M	14	Yes
4	50°	M	22	Yes
5*	40	F	38	Yes
6	38	M	24	Yes
7*	36	M	1[illegible]	Yes

*Patients with spinal anomalies.

Results

Eight of the 129 patients were excluded from the statistical analysis because of either congenital anomalies of the spine (four patients) or a skeletal dysplasia (four patients) Two of the latter patients had the Ellis-van Creveld syndrome and two the *Holt Oram syndrome* One patient with each syndrome had scoliosis in each instance the curvature was 15°

The ages of the remaining 121 patients ranged from 12 to 42 years with a mean age of 17 years, 78 per cent were between 13 and 22 years of age Thirteen patients were Negroes

Sixty five patients (54 per cent of the group) had acyanotic forms of CHD The most common types were ventricular septal defect (23) aortic stenosis (12) and atrial septal defect (10) The most common anomalies in the 56 patients with cyanotic CHD were *tetralogy of Fallot (23)* and levotransposition of the great vessels (11)

Fifty three (44 per cent) of the 121 patients had scoliosis (Table I) It was mild in 30 (25 per cent) moderate in 19 (16 per cent) and severe in 4 (3 per cent) Thirty seven (66 per cent) of the patients with cyanotic CHD had scoliosis Twenty (36 per cent) of these were mild, 13 (23 per cent) were moderate and 4 (7 per cent) were severe In contrast, only 24 per cent of the patients with acyanotic forms of CHD had scoliosis, which was mild in 15 per cent moderate in 9 per cent and severe in none Although scoliosis was more common in the group with cyanotic forms of CHD within that group there was no correlation between the hematocrit and either the frequency or the severity of scoliosis

In both the acyanotic and cyanotic groups scoliosis was more common in the females than in the males (Table I) Thirty five per cent of the acyanotic females and 19 per cent of the acyanotic males had scoliosis In the cyanotic group 80 per cent of the females and 58 per cent of the males had scoliosis

Except for two patients with the primary curvature in the lumbar spine the scoliosis was either thoracic or thoracolumbar Seven of the 129 patients had severe scoliosis (Table II) All had cyanotic forms of CHD and five were males Three of these patients were excluded from the statistical analysis because they had spinal anomalies

Table III Incidence of scoliosis in the general population

Study	No of patients	Per cent with scoliosis
A *Determined by clinical examination*		
1 Wynne Davies[4]	11 087	0 3
2 Schanz[13]	189 000	0 7
3 Medical Statistics Bulletin[9]	171 700	0 8
B *Determined by roentgenograms*		
1 Niebauer[11]	75 000	0 3
2 Morisaki et al[10]		0 7
3 Shands[12]	50 000	1 9
Patients 15 to 19 years		3 1
4 Dewar[3]	20 000	4 0
5 Wright and Niebauer[15]	200	6 0

In evaluating the onset and progression of scoliosis those with curves greater than 30° were compared with those less than 30 Average age at the onset of the scoliosis was 10 8 years in 34 patients with curves *less than 30* in the four patients with curves greater than 30° the average age of the onset of scoliosis was 6 3 years In three of these four patients the first ab*normal film* was before six years while in only one of the 34 with a curve less than 30 was it before six years Rapid progression of the scoliosis was observed in nine patients with curves less than 30 and in all four patients with curves greater than 30° The onset of rapid progression was comparable in each group—11 9 and 11 8 years respectively

The side of the aortic arch was determined in 119 patients eight of whom had right aortic arches All of the patients with right aortic arches had scoliosis and in each case the apex of the curvature was to the left Thirty seven of the patients with left aortic arches had scoliosis and in 87 per cent of these the apex of the curvature was to the right opposite the aortic arch No relationship was found between the severity of the scoliotic curvature and the side or level of the apex

Sixty seven patients had had at least one cardiac operative procedure Forty eight per cent of the patients who had had surgery had scoliosis which was moderate to severe in 21 per cent Thirty nine per cent of the patients without surgery had scoliosis which was moderate or severe in 17 per cent

Within the cyanotic and acyanotic groups no correlation was found between the specific types of CHD and either the frequency or the severity of the scoliosis nor was there any correlation between the severity of the scoliosis and the skeletal maturation

Discussion

The incidence of scoliosis in the general population is variously reported Part of the variability disappears when the series based upon physical examination are separated from those based upon roentgen examination (Table III) These studies when combined suggest that scoliosis occurs in approximately 3 per cent of the population and exceeds 10° in about 0 75 per cent

Table IV summarizes our own data and the data from four previous studies dealing with scoliosis and congenital heart disease The incidence of scoliosis varies a great deal largely as a result of the age of the patients When children of all ages were evaluated as in the studies of Luke and McDonnell[8] Wright and Niebauer[1] and Morisaki and colleagues[10] the incidence of scoliosis was lower than if only *adolescents* were considered The present study and a portion of the paper by Wright and Niebauer included only adolescents Both found a higher incidence of scoliosis

As reported by Donzelot and associates[6] and by Luke and McDonnell[8] scoliosis was considerably more common in the cyanotic than in the acyanotic patients However neither Wright nor Morisaki

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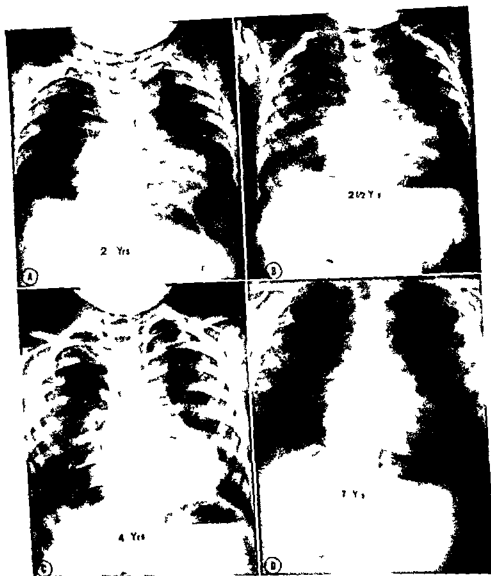


Fig 1,*A* to *F* The development of a 55° curve by the age of 13 years is demonstrated in this series of radiographs Rapid progression is seen between 7 and 10 years The patient had tetralogy of Fallot with a left sided aortic arch

it was the surgery or the aortic arch that was causing the particular convexity The present study has shown however that surgery had no effect on the incidence or the side of the scoliosis Therefore the relationship of the aortic arch and the convexity of scoliosis is noted and suggests an etiology for the scoliosis One may postulate that the spine is bowed away by the pulsations of the aortic arch and descending aorta

Fig 1 shows the development of scoliosis in a patient from no curve at 2 years to a 55° curve at 13 years Since this patient is still young his curve will probably continue to increase for some time Earlier authors stated that progression of the scoliosis stops when the iliac apophyses fuse with the crests Collis and Ponseti[2] have recently shown however that in a significant percentage of patients the scoliosis increased after apophyseal fusion They found at

Table IV. Incidence of scoliosis in CHD. Summary of data

Study	No. of patients	>5° (%)	>10° (%)
1. Donzelot et al.[4]			
Cyanotic	506	30	
Acyanotic	117	14 5	
2. Wright and Niebauer[15]	425		5 5
patients >13 years	72		19 0
3. Morisaki et al.[10]	2 715	12 5	3 3
4. Luke and McDonnell[8]			
Cyanotic	850	6 0*	
Acyanotic	2 690	0 8*	
5. Present study			
Cyanotic	56		30
Acyanotic	65		9 0

*Degree of curvature necessary to be considered scoliosis not specified but presumably at least 5°.

found such a difference. In our series, approximately one in ten acyanotic patients had a spinal curvature greater than 10° while three in ten cyanotic patients had a similar curve.

In an earlier communication we documented marked impairment of cortical bone formation in cyanotic patients.[14] This osteoporosis may contribute to the increased incidence of scoliosis in the cyanotic as compared to the acyanotic group.

While the adolescent form of idiopathic scoliosis occurs at least six times more frequently in females than in males,[6,16] the same striking sex difference does not occur in the scoliosis associated with CHD. Instead, the incidence of scoliosis was less than twice as high in the females as in the males. In the patients with curves greater than 10° the incidence was almost the same in the two sexes and five of the seven patients with curvatures greater than 30° were males.

Generally, idiopathic scoliosis is divided into three groups depending on the age of detection—infantile, juvenile, and adolescent.[7] The scoliosis associated with CHD resembles in many aspects the idiopathic type occurring in adolescence. While radiographically it may begin earlier, rapid progression of the scoliosis, when it occurred, was during adolescence. Had earlier chest radiographs not been made to assess the CHD, the scoliosis would not have been detected clinically until adolescence.

Curves beginning before six years of age were more likely to progress to severe scoliosis than were those beginning after six years. For this reason, patients who early in life develop even a mild curvature need to be assessed frequently to detect progression of the scoliosis.

No correlation was noted between the severity of the scoliosis and delayed bone maturation, hematocrit values, or the specific type of heart defect.

The only positive correlation was between the side of the aortic arch and the side of the scoliotic convexity. Most patients without CHD and a left-sided aortic arch have the major convexity of the scoliosis to the right.[8,16] Likewise, in our study there was a strong association between those with left aortic arches and right convexity scoliosis. At the same time all of the patients with a right aortic arch had a left convexity scoliosis. Luke and McDonnell[8] noted that frequently the convexity was opposite the side of the aortic arch but felt they could not dissociate it from the effect of surgery. Usually shunting procedures for cyanotic CHD are done on the side opposite the aortic arch. For this reason one could not determine whether

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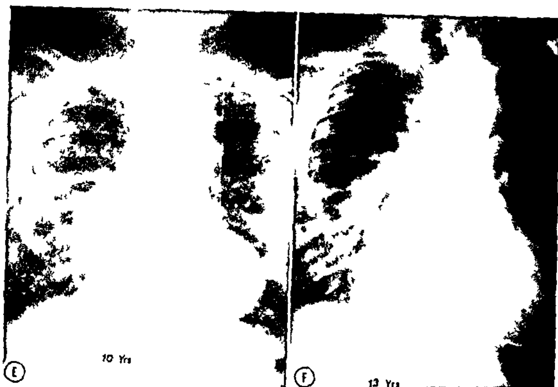


Fig 1 E and F See legend below Fig 1 A to D

least a 15° increase in the curve in 38 per cent of patients and more than 25° increase in 12 per cent It is quite possible that the patient shown in Fig 1 if left untreated, will eventually have a 100° curve

While authors vary as to how great a curve is needed before impairment of vital capacity is noted, the figures stated are in the range of 45° to 60°[2,17] Yet this is in patients with normal cardiac status Patients with cyanotic CHD are in a more precarious position and presumably will be adversely affected by even less scoliosis Four of the patients listed in Table II already have at least a 50° curve It can also be anticipated that some of the younger patients with moderate scoliosis will progress to the severe group

Summary

Scoliosis occurs with greater frequency in patients with congenital heart disease (CHD) than in the normal population In a random survey of 121 adolescent and adult patients with CHD, 44 per cent had scoliosis in 19 per cent of these patients the scoliosis exceeded 10° Patients with cyanotic forms of CHD were more commonly affected than acyanotic patients The severity of the scoliosis was also greater in the cyanotic group particularly in the male patients

While the time of clinical detection and period of rapid progression are in adolescence, the onset of the curvature radiographically begins at an earlier age Curves beginning before six years of age are the ones likely to progress to significant scoliosis

It is urged that careful attention be directed to analysis of serial chest radiographs in patients with CHD so that scoliosis can be detected and quantified and treatment can be begun when the curves show evidence of rapid progression

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The first derivative of the carotid displacement pulse

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Carefully obtained arterial pulse displacement recording closely reproduces the pressure pulse in form and timing and is therefore a useful atraumatic method Of the arterial pulses studied the carotid has been found to be most useful because of its proximity to the heart and consequently its ability to closely reflect central cardiac events Carotid pulse *contour* has been used to aid the diagnosis of aortic valve diseases and local arterial changes[1,2] while analysis of the *time relations* of the carotid pulse has been especially useful in non invasive assessment of myocardial function—e g measurement of left ventricular ejection time, pre ejection period isovolumic contraction time and pulse transmission time[3-6] Combined analysis of contour with time relationships yields a graphic and quantitative depiction of bedside examination of the carotid pulse

One important aspect of the arterial pressure pulse is its "quickness" i e the velocity of rise and fall of pressure expressed as its first time derivative or dP/dt[7,8] External arterial pulse recording reflects this as change in displacement with time which may be represented as dD/dt As with the peak of the derivative of pressure (dP/dt) the peak amplitude of the carotid displacement derivative (dD/dt) expresses the analogous maximum velocity (rate of rise) of the pulse wave

Besides supplying an important indication of pulse velocity, successful application of the first derivative of the carotid pulse would offer certain other auxiliary but important technical advantages This is because the derivative tracing tends to augment high frequency components of the pulse wave and diminish low frequency components As a result high frequency events e g small angles and notches, difficult to identify on a conventional pulse tracing are rendered more prominent and easily identifiable On the other hand low frequency disturbances, particularly unsteady baselines due to respiratory or other extrinsic movements become more stable

Because indirect carotid arterial velocity tracings have received relatively little attention we investigated the amplitude and time relationships of the carotid derivative in series of normal individuals and unselected cardiac patients and investigated the effects of different contraction strengths

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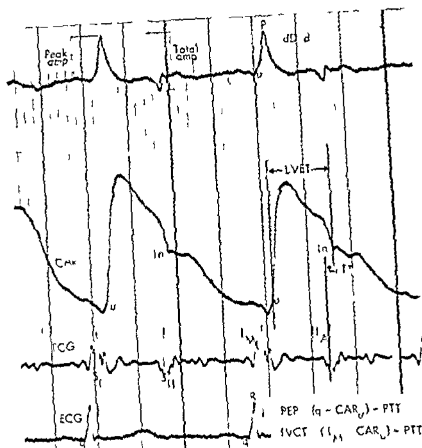


Fig 1 Top to bottom First time derivative of carotid displacement pulse (*dD/dt*) carotid pulse (*CAR*) phonocardiogram (*PCG*) Lead II electrocardiogram (*ECG*) *Amp* = amplitude *u* = upstroke *P* = peak *LVET* = left ventricular ejection time *In* = incisura *PTT* = pulse transmission time S_I = first heart sound S_{II} = second heart sound I_M = mitral component of S_I II_A = aortic component of S_{II} See text for formulas for pre ejection period (PEP) and isovolumic contraction time (IVCT)

in patients with pulsus alternans and subjects challenged with isoproterenol and propranolol

Limitations of external pulse sensors

We were aware of an obvious limitation to this approach Displacement pulse waves vary in amplitude because of physical factors which vary in individual patients and also because of differences in the pressure with which the external pulse pickup is applied The absolute size of the derivative curve is in turn dependent upon the absolute pulse wave amplitude Therefore in order to make comparisons among different individuals we have considered only the amplitude of the peak of the derivative relative to the total magnitude of the entire deflection (Fig 1)

Subjects and methods

For purposes of this investigation we studied four groups

Group I Nineteen healthy normally active but not athletically trained individuals

Group II Fifteen unselected patients with various kinds of heart disease (Table II) who were referred consecutively for study in the Clinical Cardiac Physiology Laboratory during the same period as subjects in Group I

Group III Six patients with pulsus alternans

Group IV Three subjects challenged with positive and negative inotropic agents

With the subject in the supine position the following recordings were made simul

taneously during relaxed expiratory apnea (Fig 1) (1) carotid pulse tracings using Sanborn crystal microphone No 372 with funnel type pickup applied over the right carotid artery and (2) first derivative of the carotid pulse, by passing the pulse wave through a resistance capacitance (RC) network differentiator *

Characteristics of the differentiator The circuit is a low pass filter followed by a high pass filter, both filters having the same time constant (0 001 sec) cut off at approximately 160 Hz The attenuation of the differentiation is down 20 db per decade (Thus high frequencies are accentuated and low frequencies are attenuated for all frequencies including the tenth harmonic of a rapid heart beat)

In addition to the recordings mentioned above the following measurements were also taken (3) ECG Lead II and (4) apical phonocardiogram using Sanborn contact microphone model HP 21050 A/B Recording was made on an eight channel Sanborn Photographic Recorder No 568 100A at a paper speed of 75 mm per second Ten complexes were measured in each case and the mean value taken of the following

(a) Cycle length (R R interval) from which heart rate per minute (HR) was measured
(b) Systolic intervals
  (i) *Pre ejection period* (PEP) and its components $q\ I_M$ (q of ECG to first high frequency vibration of the first heart sound), and isovolumic contraction time (IVCT) which is the interval between I_M and the rapid carotid upstroke minus the *pulse transmission time* (PTT)
  (ii) PTT was obtained by measuring the interval between the aortic component of the second heart sound (II_A) and the dicrotic notch of the carotid pulse
  (iii) Left ventricular ejection time (LVET) was measured from carotid upstroke to incisura *Ejection time index* (ETI) was measured using the formula[3] $LVET \times 1.2\ HR$ and *Corrected ejection time* $= LVET/\sqrt{RR}$
  (iv) *Carotid upstroke to peak time* and *half carotid upstroke to peak time* (t time)[9]
  (v) *Derivative upstroke to peak time* (UP)
  (vi) *Ratio of derivative peak amplitude to total derivative*—i e , peak amplitude expressed as a percentage of total amplitude

Landmarks for all these measurements are shown in Fig 1 In the patients with pulsus alternans (Group III) 10 each of consecutive strong and weak beats were measured

Results

Group I The results for Group I are summarized in Table I and Fig 2 The configuration of the carotid displacement derivative (dD/dt) closely resembled that of a pressure derivative (dP/dt) (Fig 1) Of the various relationships it will be noted that dD/dt correlated best with the pre ejection period (PEP) The correlation of dD/dt with PEP was relatively strong ($r = 0.753$ see Fig 2) and was highly significant ($p = < 0.01$) There was weak correlation with q − Im ($r = -0.481$) and with the ratio of PEP to LVET ($r = -0.463$), but these were only of borderline significance ($p \sim 0.05$) There were no significant correlations with other factors

The mean ratio of peak to total amplitude (dD/dt) was 75 ± 8 9 per cent (S D) with a standard error of 2 0 which is small (3 per cent of the mean) The mean values and standard deviations of other measurements (Table I) are well within normal limits with small standard errors and standard deviations consistent with the normal status of the subjects and their group homogeneity The PEP for example was 93 2 ± 12 9 msec (S D) with a standard error of 2 9

Group II The values for Group II for the pre ejection period and the ratio of peak to total amplitude (dD/dt) are summarized in Table II and Figure 3 The results differed markedly from those in Group I The mean PEP tended to be quite prolonged 121 4 msec (S E = 7 9) with a wide scatter compared to Group I (S D = 30 6) The ratio of peak to total amplitude (dD/dt) of 64 4 ± 1 0 per cent (S E) was clearly re

*Constructed and calibrated by Mr I Long of the NASA Electronics Research Center Cambridge Mass

Table I *Composite results in normal individuals*

Factor	Mean value	S D	S E	Correlation with amplitude ratio dD/dt r =	Significance
Amplitude ratio dD/dt	75 0%	8 9	2 0	—	—
Pre-ejection period (PEP)	93 2 msec	12 9	2 9	−0 753	P = <0 01
q Im	48 7 msec	13 5	3 1	−0 481	P ~ 0 05
PEP/LVET	0 376	0 045	0 010	−0 463	P ~ 0 05
Isovolumic contraction period (IVCT)	44 5 msec.	17 1	3 9	−0 189	ns
Heart rate	68 2 beat /min	9 9	2 3	−0 188	ns
Left ventricular ejection time (LVET)	289 3	23 6	5 4	−0 283	ns
Ejection time index (ETI)	370 9	13 6	3 1	−0 318	ns
LVET/$\sqrt{RR}$	9 7	0 39	0 09	+0 018	ns
Pulse transmission time (PTT)	38 1 msec	6 2	1 4	+0 206	ns
Carotid upstroke time	91 9 msec.	13 5	3 1	−0 239	ns
t time	27 5 msec.	5 1	1 2	−0 367	n
Derivative upstroke to peak time	29 6 msec	6 6	1 5	−0 075	ns

ns = not statistically significant.

duced but with a standard deviation of only 4 2 per cent

Group I vs Group II Per cent dD/dt differed very significantly between Groups I and II ($t = 4.24$ $P < 0.001$) Fig 3 shows no relationship between PEP and per cent dD/dt in Group II in marked contrast to Group I (Fig 2)

Group III Fig 4 depicts the results in the 6 patients with pulsus alternans The arrowheads point to the weak beats (i e beats giving rise to small pressure and displacement pulses) It is clear that the weaker beat is characterized both by marked prolongation of the pre ejection period and by a reduction in ratio of peak to total dD/dt The points on this graph show a scatter similar to that in Fig 3 but the slopes for the curves of change in each patient are very nearly parallel indicating a similar rate of changes

Group IV In three normal subjects we studied the effects of a positive inotropic agent isoproterenol (Isuprel dose 0 03 μg per minute for five minutes) A negative inotropic agent propranolol (Inderal dose 40 mg p o) was administered to two of the same subjects on a different day with studies done 2 hours after ingestion (The

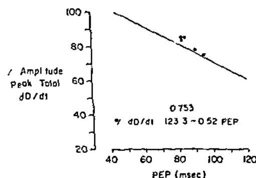


Fig 2 Normal subjects Relationship between pre ejection period (*PEP*) and ratio of peak to total amplitude of the carotid displacement pulse derivative (*dD/dt*)

third subject also received propranolol but the results were lost) Results are shown in Fig 5 *A* and *B* It is clear from this illustration that isoproterenol caused a parallel rise in dD/dt and a fall in PEP *β* blockade by propranolol produced the exact opposite effects Comparing the effects of these interventions with the natural alternation in contraction strength during pulsus alternans (Fig 4) the directional changes are strikingly similar

Table II Consecutive patients with heart disease

Patient	*% dD/dt*	*Pre ejection period*	*Diagnosis*
1	65	175	Coronary heart disease
2	60	136	Eisenmenger ventricular septal defect
3	67	101	Coronary heart disease
4	73	122	Atrial septal defect with R to L shunt
5	62	74	Hemochromatosis with heart failure
6	63	140	Cardiomyopathy (non obstructive)
7	56	160	Coronary heart disease
8	72	95	Coronary heart disease
9	65	101	Hypertensive heart disease
10	64	74	Rheumatic aortic stenosis
11	66	110	Beri beri (ethanolic) (?)
12	59	148	Coronary heart disease
13	61	115	Cardiomyopathy (non obstructive)
14	65	114	Coronary heart disease
15	63	156	Cardiomyopathy (non obstructive)
Mean	64 4	121 4	
S E	1 0	7 9	
S D	4 2	30 6	

Discussion

It has been shown by Prinzo Wilson and Kolmen[10] that the rate of rise of aortic pressure is related to the rate of development of pressure in the left ventricle Aortic dP/dt has in turn been shown to be directly related to peak blood flow velocity—i e peak left ventricular ejection rate The carotid artery is an immediate continuation of the aorta which is externally accessible and can therefore be conveniently used to detect changes in aortic pulse velocity Thus the carotid displacement pulse velocity (dD/dt) should reflect in a general way the peak rate of change in left ventricular pressure That this is highly likely is indicated by the strong statistically significant correlation between dD/dt and the pre ejection period (Table I and Fig 2) The correlation coefficient was negative so that the more rapidly ventricular contraction achieves ejection (i e the shorter the PEP) the larger the peak to amplitude ratio of dD/dt This relationship is expressed in the regression equation per cent dD/dt = 123 3 − 0 52 PEP (Fig 2)

The mean per cent dD/dt in Group I was 75 ± 8 9 per cent (S D), the mean PEP was 93 2 ± 12 msec , which is a normal figure[4 5] Indeed all the other measurements in these subjects were within normal limits Therefore, this ratio of derivative peak to total amplitude (75 per cent) can be taken to be the mean value for normal healthy adult males The small standard deviation of 8 9 suggests a small scatter and therefore a relatively narrow range of normal

The cardiac patients in Group II tended to show marked prolongation of the pre ejection period as expected in the presence of most varieties of heart disease Their ratio of peak to total amplitude dD/dt was also only 64 4 ± 1 0 per cent as compared with 75 ± 2 0 per cent for the normal individuals in Group I Much more striking is the plot in Fig 3, which clearly demonstrates the lack of relationship in the cardiac patients between PEP and per cent dD/dt Since the lower part of the range dD/dt in normals overlapped the higher values for individual patients in Group II it is the lack of relationship between per cent dD/dt and PEP which differentiates the patients as a group

That per cent dD dt can reflect the changes in contractile state implicit in changes in pre ejection period is shown in Fig 4 Pulsus alternans occurs when strong and weak beats alternate in the absence of bigeminal rhythms This ' experiment of

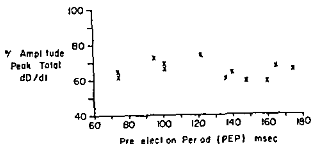


Fig 3 Patient with heart disease Relationship between pre ejection period (*PEP*) and ratio of peak to total amplitude of the carotid displacement pulse derivative (*dD/dt*) There is no correlation between per cent *dD dt* and *PEP*

...ature thus permits the patient to be his ...n control without outside interventions ...eak as compared with strong beats are ...aracterized by a large variety of changes ...ost of which document slower contractile ...elocity lower ventricular and arterial ...ystolic pressures reduced ejection time ...nd prolongation of the pre-ejection pe...iod [11 13] Our patients showed the expected ...EP prolongation for serious left ventricu...ar disease which was further exaggerated ...n the weak beats roughly in proportion to ...he fall in per cent dD/dt (slopes of curves ...n Fig 4) Similar to the *intersubject* differ...ences between Groups I and II this *intra...subject* change during pulsus alternans indi...cates that a low peak to total amplitude ...dD/dt may be associated with depression ...of left ventricular function The individual values for per cent dD/dt in strong beats and in weak beats grouped respectively without relationship to PEP (Fig 4) are entirely in keeping with the static values in Group II (Fig 3) However the changes in dD/dt between alternating strong and weak beats were strictly proportional to the corresponding changes in PEP Moreover there is a striking similarity in the slopes of the lines connecting strong and weak beats in Fig 4 with the regression line slope in Fig 2 Although the number of subjects in Group IV is small the results are in accord with these findings The directional changes after isoproterenol are in keeping with simultaneously increased contraction velocity (i e decreased PEP and increased dD/dt) those after propranolol indicate decreased contraction velocity (i e increased PEP with simultaneously decreased dD/dt)

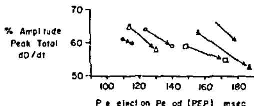


Fig 4 Patients with pulsus alternans Lines connecting the same symbols indicate changes in *PEP* and per cent *dD/dt* between strong and weak (arrow head) beats in individual patients There is a strong reciprocal correlation between changes in *PEP* and per cent *dD/dt* The near parallelism of the curves indicates similar rates of change for both factors in all patients

Conclusions and limitations

It is clear that cardiac abnormality tends to reduce the rate of rise of the carotid displacement pulse both among patients (Group II) as compared to normal individuals (Group I) and during changes in the same individuals (Groups III and IV) Moreover *as a group* cardiac patients with a variety of lesions (Table II) show depression of peak dD/dt irrespective of the degree of concomitant prolongation of the pre-ejection period — i e they are not correlated By contrast *as a group* normal individuals have lower PEP and higher per cent dD/dt and the values for these are reciprocally correlated at a high significance level ($p < 0.01$) While all the implications of these contrasting relationships are not clear it is possible that per cent dD/dt tends to reach a minimal value in the abnormal groups of 50 to 60 per cent beyond which PEP may yet increase almost indefinitely (that is the PEP changes over a wider range than does per cent dD/dt)

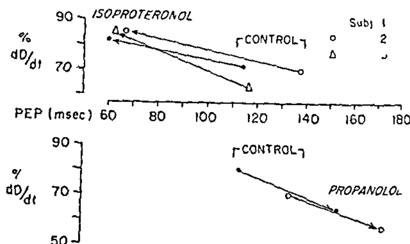


Fig 5 Top panel Effect of isoproterenol 0 03 μg/kg /min × 5 min in 3 subjects Per cent dD/dt increase as pre ejection period (*PEP*) shortens Bottom panel Effect of propranolol in subjects 1 and 2 Per cent dD/dt decreases as *PEP* lengthens

However, this limitation of the magnitude of changes in per cent dD/dt is inherent in using percentage ratios

It is clear from the foregoing that the PEP is a somewhat more sensitive index of the changes studied However per cent dD/dt appears to be of potential value in situations in which it may be difficult to obtain an accurate PEP—i e , in the absence of a satisfactory phonocardiogram or when low frequency artifacts (breathing, patient motion etc) obscure carotid pulse landmarks

Summary

The relative amplitude of the peak of the first derivative of the carotid displacement pulse (dD/dt) was obtained in 19 healthy adult males in 15 unselected, consecutively studied cardiac patients in 6 patients with pulsus alternans, and in 3 subjects challenged with isoproterenol and propranolol The group mean for normals expressed as the per cent of peak to total amplitude was 75 ± 8 9 per cent (S D) This figure can be taken as the normal range for comparable subjects There was significant and strong correlation of per cent dD/dt with the pre ejection period (PEP) among normals but no relationship at all for the group with heart disease who also tended to have markedly prolonged PEP and reduced (64 4 ± 4 2 per cent) per cent dD/dt The patients with pulsus alternans showed no relationship between per cent dD/dt and PEP for either strong or weak beats but showed a striking association between the directional changes in per cent dD/dt and PEP These were reciprocal with marked parallelism in the rate of change for all patients Isoproterenol increased per cent dD/dt and decreased PEP Propranolol had an opposite effect Reduced per cent dD/dt therefore is associated with depression of left ventricular function

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Serum enzyme levels during exercise in patients with coronary heart disease: Effects of training

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Elevation of certain serum enzymes has been reported after muscular exercise. Serum lactate dehydrogenase (LDH) has been reported to rise acutely after muscular exercise in man.[1] In untrained rats elevations of serum LDH and its isoenzymes also occur, these changes being abolished by physical conditioning.[2] Creatine phosphokinase (CPK) levels have also been found to increase 24 hours after exercise in man.[3]

The release of LDH or CPK may reflect cell necrosis and/or transudation of LDH or CPK from intracellular to extracellular compartments. Since each is contained in both myocardium and skeletal muscle, knowledge of the tissue or tissues responsible for their release may prove helpful in the interpretation of serum elevations detected in relation to the stress of muscular exercise.

LDH is found in many body tissues. Its isoenzymes are distributed more specifically. LDH 1 forms the major LDH component of myocardium and kidney.[4] LDH 2 is the major component in kidney, lesser amounts being found in myocardium and several other tissues.[4] LDH 3 is found in the lung.[5] LDH 4 and 5 predominate in skeletal muscle, liver, red blood cells, and platelets.[4,6] CPK is found predominantly in skeletal and cardiac muscle.[7]

In this study the serum concentration of LDH and its isoenzymes and CPK were measured in patients with coronary artery disease before, during, and after leg exercise. The effects of physical conditioning were examined.

Methods

All subjects accepted into the study were male and had coronary atherosclerosis documented either by coronary arteriography or by accepted clinical criteria (classical effort related angina pectoris with a positive electrocardiographic (ECG) exer

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Table I En yme changes in untrained subjects

Baseline	*n*	*Rest*	*Exercise*	*P*
Total LDH concentration	10	107 9 ± 5 0	119 2 ± 6 5	<0 001
% LDH 1	11	28 6 ± 1 8	26 3 ± 1 9	<0 001
% LDH 5	11	11 3 ± 1 1	12 9 ± 1 2	<0 01
LDH-1 concentration	10	29 7 ± 1 8	29 4 ± 1 4	NS
LDH-5 concentrat on	10	12 1 ± 1 6	15 2 ± 1 8	<0 001
CPK†	6	28 6 ± 11 9	27 0 ± 14 3	NS

Baseline	*n*	*Rest*	*5 minutes post exercise*	*P*
Total LDH concentration	7	111 4 ± 6 6	13? 6 ± 21 8	NS
% LDH 1	7	25 1 ± 1 6	24 9 ± 3 1	NS
% LDH 5	7	10 5 ± 1 ?	14 8 ± 2 1	<0 0?
LDH-1 concentration	7	28 0 ± 2 2	31 5 ± 4 4	NS
LDH-5 concentration	7	12 0 ± 1 8	19 7 ± 4 0	<0 05
CPK	6	28 6 ± 11 9	33 1 ± 8 8	NS

La t t d l yd genase co ce tratio n Wacke ts.
†C t ne ph ph k nase co ce trat I nt rn tional ts
‡NS = t t t tically ig fica t

cise test) Their ages ranged from 41 to 61 years All were leading a sedentary life at the time of the study

Three studies were performed in a total of 21 patients

Study I Eleven patients underwent an initial study at rest and during exercise on a graduated bicycle ergometer Blood samples were obtained from an indwelling brachial arterial cannula at rest at the peak level of effort achieved and (in seven subjects) five minutes after cessation of exercise Five of these subjects subsequently underwent a supervised program of physical conditioning for 6 to 12 weeks and were then retested Conditioning was carried out on the same bicycle ergometer utilized for testing The subjects exercised for a minimum of 25 minutes three days per week with work loads increased at weekly intervals

Conditioning was documented by a decrease in heart rate noted at rest and at all levels of exercise and by an increase in peak work load achieved

Study II Five other sedentary subjects with atherosclerotic heart disease were studied at the time of diagnostic cardiac catheterization Arterial and coronary sinus (CS) levels of LDH and LDH isoenzymes were recorded at rest and during supine leg exercise on a bicycle ergometer

Study III Five additional subjects had venous levels of LDH LDH isoenzymes and CPK determined at rest before exercise testing Repeat measurements were then obtained 24 hours after the test

In all instances the end point for the exercise test was the appearance of either angina pectoris or physical exhaustion

Total LDH concentration was measured by the automated procedure of Passen and Gennaro[3] and was reported in Wacker units The per cent of this total represented by the isoenzymes of LDH was determined by application of 1 25 ml of serum to Gelman Sepraphore III strips at pH 8 4 in a Tris HCl barbiturate buffer using a Beckman R101 microzone electrophoresis cell Activity staining was performed in agar plates containing lactate NAD nitro blue tetrazolium dye and phenazine metho sulfate After incubation fixation was achieved with 3 per cent nitric acid the membranes were dried and then read at 600 nm on a densitometer Paired samples were drawn for every observation and each was then analyzed in duplicate Four values therefore were averaged for each measurement CPK was measured on the day

of each study by the technique of Nuttall and Wedin,[9] and reported in international units (I U)

Except where otherwise stated, statistical analyses were performed by the 't' test for paired data [10]

Results

I *Baseline studies* Arterial total LDH (in units) increased significantly from the rest state to peak exercise (107 9 ± 5 0 to 119 2 ± 6 5 SE p < 0 001) and to 132 6 ± 21 8 five minutes after peak effort was discontinued (see Table I) However, the myocardial fraction (LDH 1) actually fell during exercise from a mean of 28 6 ± 1 8 per cent to 26 3 ± 1 9 per cent p < 0 001 Expressed as absolute values for LDH 1 concentration no significant change was noted comparing control values to exercise or to the post exercise determinations (see Table I)

Of the 11 patients performing baseline studies, 6 developed angina and ST segment depression while 5 developed only ST segment depression on the ECG The changes in LDH and LDH 1 concentration were identical in those patients with and without angina

The per cent observed for LDH 5 the isoenzyme predominantly located in skeletal muscle liver, red blood cells and platelets did rise both from rest to exercise (11 3 ± 1 1 to 12 9 ± 1 2 per cent p < 0 01) and from rest to post exercise (10 5 ± 1 2 to 14 8 ± 2 1 per cent p < 0 02) LDH 5 concentration rose from 12 1 ± 1 6 units at rest to 15 2 ± 1 8 units (p < 0 001) during exercise Post exercise a concentration of 19 7 ± 4 0 units (p < 0 05 compared to rest) was observed No significant changes were noted in arterial levels of CPK or in LDH 2 3 and 4

RESTUDIES AFTER CONDITIONING The clinical effects of conditioning were significant as judged by an increase in the peak effort achieved from 530 ± 53 9 kilopond meters (kpm)* per minute to 710 ± 55 7 kpm per minute p < 0 001 In addition though peak effort had been limited by angina in 3 of 5 instances before conditioning effort was terminated by fatigue without angina, in all 5 subjects restudied after conditioning

The rise in total LDH concentration significant at the 0 001 level before conditioning, was slightly attenuated by conditioning p only < 0 05 (see Table II) By 5 minutes after peak effort the concentration of LDH had fallen to control levels (Table II) in these conditioned patients

In Table III, the *changes* in total LDH and LDH 5 concentrations observed with exercise before conditioning are compared to those observed after conditioning Before training, total LDH rose 11 4 ± 2 9 units (from 107 9 ± 5 0 to 119 2 ± 6 5) during exercise The level rose 10 8 ± 4 0 units (from 110 4 ± 5 7 to 121 2 ± 6 1) after conditioning These changes are similar as were the changes from rest to post exercise

The mean increase in LDH 5 concentration however was 3 1 ± 0 7 (12 1 ± 1 6 to 15 2 ± 1 8) before and only 0 9 ± 0 4 units (11 2 ± 1 1 to 12 0 ± 1 2) after training p < 0 01 The increase in LDH 5 concentration from rest to post exercise, 7 7 ± 3 8 (12 0 ± 1 8 to 19 7 ± 4 0) before conditioning, was significantly decreased (p < 0 05) to only 0 3 ± 0 8 (11 2 ± 1 1 to 11 5 ± 0 1) by training

II *Catheterization studies* Total arterial LDH rose from 120 8 ± 10 9 to 152 1 ± 11 0 units p < 0 001 and arterial LDH 1 concentration rose from 29 9 ± 1 9 to 39 1 ± 3 0 (p < 0 01) during exercise (see Table IV) However no significant change was noted in arterial per cent LDH 1 Nor was there a significant difference between the arterial and coronary sinus LDH concentrations (Table IV) or in the arterial compared to the coronary sinus percentage of any isoenzymes Thus mean myocardial production of LDH 1 was not seen even though in three studies leg exercise was associated with angina pectoris

III *24 hour studies* Twenty four hours after an exercise stress sufficient to cause angina or exhaustion in 5 patients with coronary artery disease no significant change in venous levels of either LDH LDH isoenzymes or CPK was noted (Table V)

Discussion

The data reported above show that sedentary patients with coronary heart disease

* 1 kilopond meter (kpm) = the force acting on the mass of 1 kg at normal acceleration of gravity 1 kpm = 9 80665 joules 6 kpm = 1 watt

Table II Enzyme changes after conditioning (n = 5)

Baseline	Rest	Exercise	Post exercise
Total LDH concentration	110 4 ± 5 7	121 2 ± 6 1‡	117 0 ± 7 0
% LDH 1	23 5 ± 2 9	22 4 ± 2 1	23 1 ± 2 5
% LDH 5	10 2 ± 0 8	10 0 ± 0 9	10 0 ± 0 9
LDH 1 concentration	25 9 ± 3 4	26 9 ± 2 0	26 7 ± 2 5
LDH 5 concentrat on	11 2 ± 1 1	12 0 ± 1 2	11 5 ± 0 7
CPK†	20 3 ± 3 9	21 8 ± 6 2	20 4 ± 5 1

L ct t d hyd g se conce trat in W ck unit
†C eatine phosph kinase co ce trat on, in I ternational ta.
‡p < 0 05 compared t rest. All ther val s show no s gnifica t diff ce f m rest g levels.

Table III Comparison of changes in enzyme levels observed with exercise before and after conditioning (n = 5)

Rise in total LDH	Before conditioning	P†	After conditioning
Rest to exercise	11 4 ± 2 9	NS‡	10 8 ± 4 0
Rest to post-exercise	21 1 ± 16 5	NS	6 5 ± 6 2

Rise in total LDH 5	Before conditioning	P†	After conditioning
Rest to exercise	3 1 ± 0 7	<0 01	0 9 ± 0 4
Rest to post-exercise	7 7 ± 3 0	<0 05	0 3 ± 0 8

*Lact t d hydrog nase co ce trat i Wacke nits.
† t t f u pa d d ta.
‡NS = t st tistically sig ifica t.

can exercise to the limits of their tolerance without detectable efflux of CPK or LDH 1 from the myocardium Although total LDH concentration did rise during acute exer cise the values observed were still within the limits of normal Furthermore coro nary sinus sampling failed to demonstrate myocardial production of LDH or any of its isoenzymes The rise must have been derived from peripheral tissues

Indeed a significant elevation of arterial LDH 5 concentration was noted in these patients This is consistent with release from skeletal muscle liver red blood cells or platelets[4] CPK predominantly found in skeletal muscle did not rise significantly suggesting that the source of LDH may have been other than skeletal muscle or that CPK release requires a greater stress

A program of physical conditioning abol ished the release of LDH 5 during exercise in our patients This is suggestive evidence for an effect of conditioning upon blood flow or energy utilization in skeletal mus cle liver and/or formed blood elements the chief sources of this isoenzyme Var nauskas and co workers[11] have shown de creased blood flow and increased levels of respiratory enzymes in skeletal muscle of healthy volunteers after physical training

It would appear that the prevention of detectable enzyme release during exercise is dependent not only on the level of condi tioning but upon the severity of the stress imposed We have previously reported[12] LDH 5 elevations in trained athletes after a 10 000 meter run Nuttall and Jones[3] have reported rises in CPK when normal volun teers were stressed by weight lifting This finding not seen in our patients performing bicycle exercise was then abolished by a conditioning program

LDH elevations during exercise in un trained rats have been reported by Garbus

of each study by the technique of Nuttall and Wedin,[9] and reported in international units (I U)

Except where otherwise stated statistical analyses were performed by the t test for paired data[10]

Results

I *Baseline studies* Arterial total LDH (in units) increased significantly from the rest state to peak exercise (107 9 ± 5 0 to 119 2 ± 6 5 SL p < 0 001) and to 132 6 ± 21 8 five minutes after peak effort was discontinued (see Table I) However the myocardial fraction (LDH 1) actually fell during exercise from a mean of 28 6 ± 1 8 per cent to 26 3 ± 1 9 per cent p < 0 001 Expressed as absolute values for LDH 1 *concentration no significant change* was noted comparing control values to exercise or to the post exercise determinations (see Table I)

Of the 11 patients performing baseline studies 6 developed angina and ST segment depression while 5 developed only ST segment depression on the ECG The changes in LDH and LDH 1 concentration were identical in those patients with and without angina

The per cent observed for LDH 5 the isoenzyme predominantly located in skeletal muscle, liver red blood cells and platelets did rise both from rest to exercise (11 3 ± 1 1 to 12 9 ± 1 2 per cent, p < 0 01) and from rest to post exercise (10 5 ± 1 2 to 14 8 ± 2 1 per cent p < 0 02) LDH 5 concentration rose from 12 1 ± 1 6 units at rest to 15 2 ± 1 8 units (p < 0 001) during exercise Post exercise a concentration of 19 7 ± 4 0 units (p < 0 05 compared to rest) was observed No significant changes were noted in arterial levels of CPK or in LDH 2 3 and 4

RESTUDIES AFTER CONDITIONING The clinical effects of conditioning were significant as judged by an increase in the peak effort achieved from 530 ± 53 9 kilopond meters (kpm)* per minute to 710 ± 55 7 kpm per minute p < 0 001 In addition, though peak effort had been limited by angina in 3 of 5 instances before conditioning, effort was terminated by fatigue, without angina in all 5 subjects restudied after conditioning

The rise in total LDH concentration significant at the 0 001 level before conditioning, was slightly attenuated by conditioning, p only < 0 05 (see Table II) By 5 minutes after peak effort, the concentration of LDH had fallen to control levels (Table II) in these conditioned patients

In Table III, the *changes* in total LDH and LDH 5 concentrations observed with exercise before conditioning are compared to those observed after conditioning Before training total LDH rose 11 4 ± 2 9 units (from 107 9 ± 5 0 to 119 2 ± 6 5) during exercise The level rose 10 8 ± 4 0 units (from 110 4 ± 5 7 to 121 2 ± 6 1) after conditioning These changes are similar as were the changes from rest to post exercise

The mean increase in LDH 5 concentration however, was 3 1 ± 0 7 (12 1 ± 1 6 to 15 2 ± 1 8) before, and only 0 9 ± 0 4 units (11 2 ± 1 1 to 12 0 ± 1 2) after training p < 0 01 The increase in LDH 5 concentration from rest to post exercise 7 7 ± 3 0 (12 0 ± 1 8 to 19 7 ± 4 0) before conditioning was significantly decreased (p < 0 05) to only 0 3 ± 0 8 (11 2 ± 1 1 to 11 5 ± 0 7) by training

II *Catheterization studies* Total arterial LDH rose from 120 8 ± 10 9 to 152 1 ± 11 0 units p < 0 001 and arterial LDH 1 concentration rose from 29 9 ± 1 9 to 39 1 ± 3 0 (p < 0 01) during exercise (see Table IV) However no significant change was noted in arterial per cent LDH 1 Nor was there a significant difference between the arterial and coronary sinus LDH concentrations (Table IV) or in the arterial compared to the coronary sinus percentage of any isoenzymes Thus mean myocardial production of LDH 1 was not seen even though in three studies leg exercise was associated with angina pectoris

III *24 hour studies* Twenty four hours after an exercise stress sufficient to cause angina or exhaustion in 5 patients with coronary artery disease no significant change in venous levels of either LDH LDH isoenzymes or CPK was noted (Table V)

Discussion

The data reported above show that sedentary patients with coronary heart disease

*1 kilopond meter (kpm) = the force acting on the mass of 1 Kg at normal acceleration of gravity 1 kpm = 9 80665 joules 6 kpm = 1 watt

befor and after a conditioning program in 11 patients with coronary artery disease Myocardial A V differences of LDH were also obtained during exercise in 5 patients No significant elevation of the arterial myocardial LDH fraction (LDH 1) or of CPK was seen during exercise In the un trained subjects arterial LDH 5 concen tration rose during exercise before training This rise was attenuated by the training program Myocardial production of LDH its isoenzymes or CPK was not found even during exercise producing anginal pain

These data suggest that tolerable exer cise does not cause significant myocardial injury Evidence for a peripheral effect of conditioning is deduced from changes in LDH 5 re ponse to exercise

The authors acknowledge with gratitude the efficient secretarial assistance of Mrs Mary Richard son Mrs June B Coons and Mrs Kathy Pella.

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Table IV Transmyocardial LDH gradients

Patient	Rest						Exercise					
	Total LDH†		LDH 1		LDH 5		Total LDH		LDH 1		LDH 5	
	Artery	CS‡	Artery	CS	Artery	CS	Artery	CS	Artery	CS	Artery	CS
1	129	117	29 7	26 4	23 3	14 3	142 5	156	31 2	33 2	20 [illegible]	33 7
2	81	88	25 7	29 1	6 3	6 7	115	124	3[illegible] 4	35 7	13	12 6
3 *	117	123	25 7	23 4	15 8	11 1	159	114	42 1	24 5	21 5	14 8
4 *	144	147	28 9	39	14 4	14	171	102	44 5	26 5	18	11 2
5 *	133	107	35 9	32 1	10 6	8 6	174	120	45 2	30 6	14 8	13 8
Mean	120 8	116 5	29 2	30 0	14 1	10 9	152 1	123 2	39 1	30 1	17 5	17 2
SE	±10 9	±9 7	±1 9	±2 7	±2 8	±1 5	±11 0‖	±9 0	±3 0§	±2 1	±1 6	±4 2

*Angina during exercise
†Lactate dehydrogenase concentration in Wacker units
‡Coronary sinus
§p < 0 01 compared to arterial level at rest
‖p < 0 001 compar d to arterial LDH concentration at r t There were no ot r significant differences noted between arterial level rest and exerci e nor was there a significant myocard al A V difference of total LDH or isoenzyme fraction

Table V Enzyme levels 24 hours after exercise (n = 5)

Variables	Before exercise	After exercise	P
Total LDH*	119 4 ± 14 7	97 8 ± 17 4	NS‡
% LDH 1	21 0 ± 1 5	20 2 ± 0 9	NS
% LDH 5	11 8 ± 0 6	13 6 ± 1 3	NS
CPK†	46 7 ± 12 1	36 2 ± 22 3	NS

*Lactate dehydrogenase concentration in Wacker units
†Creatine phosphokinase concentration in international units.
‡NS = not stati tically significant

Highman and Altland[2] They found that prolonged effort produced elevations of LDH 5 (and 1 and 2) These changes were correlated with fatty infiltration and cell necrosis in the myocardium exercised skele tal muscle, kidney liver and adrenal glands of these rats The serum enzyme and patho logical changes were not observed after exercise in trained rats Attenuation of LDH release during effort has also been caused by conditioning of rats in the studies of Papadopoulos Leon and Bloor[4 6] Fow ler and associates[1] also noted larger serum enzyme elevations in untrained human volunteers than in conditioned human vol unteers

The most significant implication of our data is derived from the absence of an elevation of the myocardial LDH fraction or of CPK during tolerable levels of exer cise in coronary patients This admittedly crude assay suggests that tolerable exercise itself does not necessarily produce myo cardial injury or necrosis This is reassuring evidence in the light of expanding interest in physical conditioning programs for pa tients with coronary artery disease[13] Sup portive evidence is supplied for an improve ment in blood flow or in the intermediary metabolism of peripheral tissues after training

Summary

Arterial lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) levels were measured at rest and during exercise,

before and after a conditioning program in 11 patients with coronary artery disease Myocardial A V differences of LDH were also obtained during exercise in 5 patients No significant elevation of the arterial myocardial LDH fraction (LDH 1) or of CPK was seen during exercise In the un trained subjects arterial LDH 5 concen tration rose during exercise before training This rise was attenuated by the training program Myocardial production of LDH its isoenzymes or CPK was not found even during exercise producing anginal pain

The e data suggest that tolerable exer ci e does not cause significant myocardial injury Evidence for a peripheral effect of conditioning is deduced from changes in LDH 5 response to exercise

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A complication of the Fogarty arterial embolectomy catheter

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Previously reported complications of the Fogarty arterial embolectomy catheter have consisted of rupture of the artery by the inflated balloon, arterial perforation by the tip of the catheter, creation of an arterial venous fistula, tear or disruption of the intima, and balloon rupture with embolization of a fragment of rubber.[1] The major problem of the balloon catheter has been balloon breakage. However, the balloon has been deliberately made fragile so as to rupture prior to the point where pressure would damage the vessel.[3] A previously unreported complication of the Fogarty catheter has resulted from the construction of the metal coil spring tip that is present in the No. 2 and No. 3 French Fogarty arterial embolectomy catheter. Similar tips are present on the Fogarty venous thrombectomy catheter, the biliary balloon probe, and the dilation catheter for atrial septostomy.*

In two patients the No. 3 French Fogarty arterial embolectomy catheter was used to remove clots from the brachial artery following cardiac catheterization.[4] Resistance was found on pullback of the catheter in the artery. The balloon had broken in both cases and the stainless steel wire in the tip of the ballon had become embedded in the arterial wall and unwound from the tip of the catheter. In one patient this complication occurred approximately 4 cm. distal to the brachial arteriotomy in the antecubital fossa and the skin incision was extended distally over the artery to remove the tip of the catheter. The tip of the wire was embedded in the arterial wall under an atherosclerotic plaque but the catheter had not perforated the artery. A second arteriotomy was performed at the point were the wire was embedded. The wire was disengaged and the proximal catheter was cut away at the site of the original arteriotomy. The remaining catheter was removed through the distal arteriotomy. In the second patient the wire unwound from the catheter in an interosseous artery in the distal forearm resulting in the deposition of foreign bodies—i.e., the stainless steel wire, the natural rubber (latex) balloon, the Dacron suture which is used to bind the balloon to the catheter body, and the small quantity of epoxy that is used at the coil tip within the balloon and to cover the suture wiring. This patient has been followed for a period of eight months and has developed neither signs nor symptoms related to the remaining foreign bodies (see Fig. 1).

Separation of the tip of the catheter has been reported previously by Hogg and

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*Edwards Laboratories, Division of American Hospital Supply Corporation: Personal communication, December 1971.



Fig 1 Distal right forearm roentgenogram showing the separated coiled wire from the Fogarty arterial embolectomy catheter

MacDougall[6] but no additional information was given Hunter Sessions and Buenger[8] have reported experimental obstruction of the inferior vena cava in dogs with a balloon catheter for a period up to two years which resulted in local fibrosis and thickening of the vein at the point of the balloon contact There was normal architecture of the adjacent segments of vena cava and no evidence of infection Foster and colleagues[1] have reported vascular obstruction secondary to balloon breakage and distal embolization which was symptomatic and ultimately required amputation of the lower extremity

Because of the potential complications from balloon emboli it is important to avoid excessive traction on pullback of the metal coil spring tipped catheter Whenever significant resistance is met deflation of the balloon is recommended followed by a second attempt at pullback If resistance is still met a short waiting period of 10 to 15 minutes should be allowed for relaxation of any arterial spasm and then pullback should be attempted again If the catheter cannot be removed following these procedures an x ray should be taken to see whether the metal wire is unwinding from the tip of the catheter If the wire appears intact as noted in Fig 2 *A* pressure

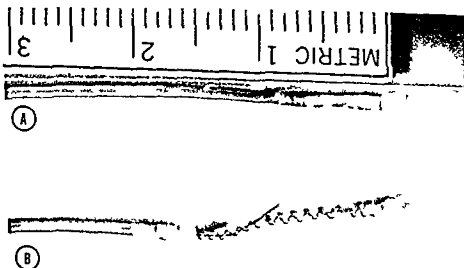


Fig 2 *A* and *B* Photographs of the No 3 French Fogarty arterial embolectomy catheter *A* Catheter metal coil spring tip intact *B* Metal coil spring tip of the catheter unwinding

should be reapplied and the catheter pulled back approximately 1 cm and the x-ray should then be repeated. If the wire is unwinding as noted in Figure 2,*B* the patient should have an arterial cutdown over the site of the wire, the proximal portion of of the catheter should be cut away and the rest of the catheter removed distally to prevent the occurrence of a foreign body or possible embolus with vascular obstruction.

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Experimental and laboratory reports

The effect of hypoxia on the coronary blood flow in reserpinized dogs

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It is known from the work of several authors that coronary blood flow increases with a lowering of the oxygen content of the blood In intact anesthetized dogs it has also been shown that coronary blood flow heart rate and mean aortic blood pressure remain elevated during a 2 hour period of continuous hypoxemia and that the increment of coronary blood flow was much g eater than that of the heart rate and blood pressure [1] As to the mechanism of such a strong coronary vasodilation of hypoxemia Berne and colleagues and Guz and associates[3] showed the importance of myocardial tissue hypoxia Furthermore from studies on isolated heart preparations Katori and Berne[4] reached the conclusion that coronary vasodilation was caused by a change in myocardial metabolism However Katz Katz and Williams[5] observed that coronary blood flow changes spontaneously even when the oxygen tension of the circulating blood and intracardiac factors such as heart rate aortic blood pressure and cardiac output were kept constant They emphasized the probable action of the nervous system and humoral agents on the coronary circulation In fact catecholamines which are known to be both mediators of the sympathetic nervous system and also one of the humoral agents cause changes not only in coronary blood flow and aortic blood pressure but also in myocardial metabolism [6,7] Thus catecholamines have effects on the cardiac activities similar to those observed under hypoxemia Consequently the question has arisen as to whether the coronary vasodilatory effect of hypoxemia by means of metabolic change might be mediated to a large extent by catecholamines in the myocardium

In the present study an attempt has been made to distinguish the direct effect of hypoxemia from the actions of catecholamines Coronary blood flow has therefore been measured in reserpinized dogs in which the effects both of catecholamines and of the sympathetic nerves are thought to disappear [8] In such dogs it was expected that the effect of hypoxemia would become very small if it is normally mediated by catecholamines

For determination of the coronary blood flow a covered hydrogen catheter electrode[1] was employed By use of this electrode the effect of hypoxemia on coronary blood flow was safely observed even in reserpinized dogs under a severe hypoxemia since the electrode method has the

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advantage of requiring neither blood sampling nor surgical opening of the chest.

Method

The H_2 catheter electrode and the procedure required to introduce it into the coronary sinus have been described in previous papers.[1,9,10] The coronary blood flow was calculated according to Fick's law from the H_2 desaturation or clearance curves.[1,11] Therefore, the coronary blood flow under investigation was not the instantaneous blood flow but rather the average blood volume flowing through a unit volume of tissue in unit time. The values were expressed as milliliters per 100 ml. per minute. Coronary vascular resistance was obtained by dividing the mean aortic blood pressure by the coronary blood flow:

$$\frac{\text{mm Hg}}{\text{milliliters per 100 ml. per min.}}$$

Fifteen mongrel dogs were treated with reserpine (1 mg. per kilogram of body weight), the dose being divided into 4 parts each consisting of 0.25 mg. per kilogram of body weight. The drug was injected intramuscularly over a period of three days. When severe dehydration of the dogs was noted during the course of treatment, 100 to 150 ml. of a 20 per cent glucose Ringer's solution was injected intravenously. The dogs were used in the experiments approximately 15 hours after the final injection of reserpine. They were anesthetized by intravenous injection of sodium pentobarbital in a dose of 10 mg. per kilogram of body weight and heparinized with 120 United States Pharmacopeia (U.S.P.) units per kilogram of body weight. One catheter electrode was introduced into the coronary sinus by way of the exposed right jugular vein and another was introduced into the thoracic aorta through the right femoral artery. Two dogs were given an intravenous injection of 0.5 mg. per kilogram of body weight propranolol prior to the blood flow measurements. Respiration was maintained with a positive pressure respiratory pump through a J-valve and cannula inserted in the trachea. The ventilation volume was 250 ml. per kilogram per minute. Air and the following three gas mixtures were alternatively breathed: (1) 21.60 per cent O_2, 4.0 per cent H_2, and 74.40 per cent N_2, (2) 6.72 per cent O_2 and 93.28 per cent N_2 without H_2, and (3) 6.71 per cent O_2, 4.11 per cent H_2, and 89.18 per cent N_2. These gas mixtures were prepared by mixing commercial O_2, H_2, and N_2 gases and they were stored in high pressure cylinders. O_2 concentrations of the mixtures were determined by use of Scholander's gas analyser and H_2 concentrations were determined by gas chromatography. The gas mixtures were introduced separately into three spirometers which were connected with the tracheal cannula by means of a 3-way tap.

The registration of H_2 saturation and desaturation was carried out sequentially in the following stages using the three gas mixtures and air for breathing: (1) control measurement with air breathing and spontaneous heart rate, (2) pacemaking of the heart rate at 180 beats per minute and air breathing, and (3) pacemaking of the heart rate at 180 beats per minute and breathing the No. 2 gas mixture (see preceding paragraph).

The details of each recording were as follows:

(1) Registration was started during steady breathing of air. Then the 3-way tap was turned to the No. 1 gas mixture. With H_2 inhalation the H_2 current increased to attain a plateau showing a saturation point. The 3-way tap was then returned to room air. H_2 was washed out gradually and the desaturation curve was recorded. Throughout this procedure the control value of the coronary blood flow was obtained.

(2) The heart rate was fixed at a higher rate of 180 beats per minute by an electrical stimulator, and the procedure described in (1) was repeated.

(3) Next, the No. 2 gas mixture was breathed from a spirometer. The arterial blood pressure reached a quasi-stable state approximately ten minutes after the onset of hypoxia and then the 3-way tap was switched to another spirometer containing the No. 3 gas mixture. In four to five minutes the H_2 curves attained a plateau. Then, the inspiratory control tap was returned to the No. 2 gas mixture.

From the desaturation curves obtained by this procedure the coronary blood flow

J I me 84
N mb 4

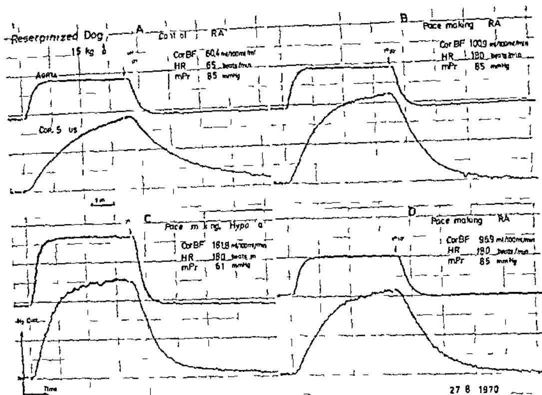


Fig 1 1 through D An example of the actual record ng of H_2 curves in the aorta (*upper* curve) and coronary s nus (*lower* curve) of a reserpinized dog under the three following cond tions *A* room air breathing (*RA*) and spontaneous heart rate for *control* *B* pacemaking at 180 beats per minute during air breathing *C* pacemaking during hypoxia breathing (*Hypoxia*) *D* pacemaking during air breathing the same condition as in *B* *CorBF* *HR* and *mPr* denote the coronary blood flow heart rate and mean aortic blood pressure re pectively

under hypoxia and pacemaking was obtained In some dogs stage 2 was excluded so that the effect of hypoxia could be tested without pacemaking In other dogs the relation between heart rate and coronary blood flow was examined under room air breathing In these cases the third stage was excluded Five minutes after the setting of a new heart rate procedure 2 was repeated When the No 2 gas mixture was breathed with the fixed ventilation volume the arterial Po_2 and Pco_2 on average were found to be 33.5 and 38.5 mm Hg respectively in the two reserpinized dogs under hypoxia

The electrical pacemaker of the heart generated a square wave pulse of 2.5 v and 2 msec duration at a frequency of 120 to 290 cycles per minute Two thin silver rings were attached to the tip of a Kifa s green heart catheter From each ring a wire was led through the catheter lumen and connected to the pacemaker The tip of this catheter was introduced into the right atrium by way of the exposed left femoral vein A polyethylene tube was inserted from the left femoral artery into the thoracic aorta to measure the aortic blood pressure This was recorded by use of a RP 2 electric transducer and a polygraph * The mean aortic blood pressure was obtained by electric integration Another polyethylene tube was placed in the abdominal vein through the right femoral artery in order to inject additional pentobarbital and heparin when necessary

Results

Fig 1 shows actual recordings from the reserpinized dogs Two H_2 curves for the aorta and coronary sinus are shown from top to bottom In Fig 1,A are shown the

* Manuf ctu d by N o kohd n Co T kyo Japan.

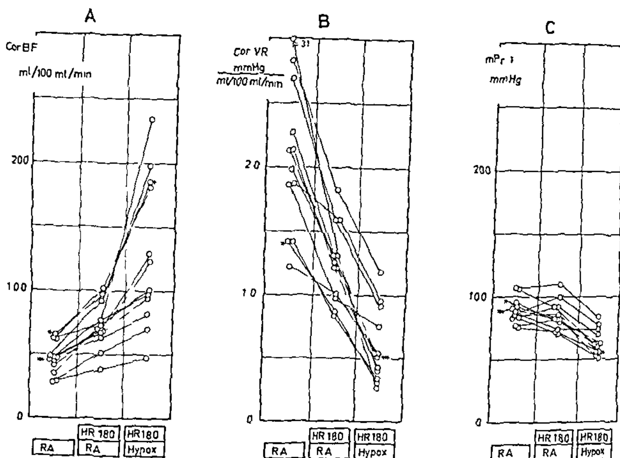


Fig. 2. *A*, *B*, and *C*. All of the obtained values of coronary blood flow (*A*), coronary vascular resistance (*B*), and mean aortic blood pressure (*C*) under the same three conditions as in Fig. 1. *RA*, *Hypox*, and *HR 180* denote *room air breathing*, hypoxia breathing, and pacemaking at a rate of 180 beats per minute. The asterisks indicate the serial measurements after the treatment with propranolol.

H_2 curves obtained during air breathing (stage 1). The heart rate and mean aortic blood pressure were 65 beats per minute and 85 mm. Hg, which are both remarkably low in comparison with nonreserpinized dogs. The change of the H_2 curve of the coronary sinus was slow, from which the coronary blood flow was calculated as 60.4 ml. per 100 ml. per minute. In the second stage the heart rate was increased to 180 beats per minute by use of the pacemaker. Under this induced tachycardia the mean aortic blood pressure remained unaltered. But as seen in Fig. 1,*B*, the H_2 curve in the coronary sinus became steeper than in the control in Fig. 1,*A*, and the coronary blood flow increased from the control value of 60.4 to 100.9 ml. per 100 ml. per minute. Then, in stage 3, hypoxia was imposed on the dog whose heart rate was fixed electrically at the previous high level of 180 beats per minute. The hypoxia caused a decrease in the mean aortic blood pressure from 85 to 61 mm. Hg. But, as clearly seen in Fig. 1,*C*, the H_2 curve changed more rapidly than that shown in Fig. 1,*B*. The coronary blood flow that was previously increased by tachycardia was further elevated from 100.9 to 181.8 ml. per 100 ml. per minute by hypoxia. The H_2 curves shown in Fig. 1,*D*, were obtained when inspired gas for respiration was returned to room air while the pacemaking was still maintained—i.e., the experimental conditions were returned to those of Fig. 1,*B*. Under these conditions the coronary blood flow was reduced from the maximum value obtained in Fig. 1,*C*, to 96.6 ml. per 100 ml. per minute, which is within 5 per cent of the value shown in Fig. 1,*B*.

Fig. 2 summarizes all the values obtained by 12 measurements in 6 dogs for coronary blood flow, coronary vascular resistance, heart rate, and mean aortic blood pressure. The abscissa shows the above three sequential treatments. The electrically induced tachycardia increased the coronary blood flow in all dogs ($p < 0.01$), while

Table I Hemodynamic measurements with pacemaking under normoxia and hypoxia in experimental and control dogs

Variables	Control		Pacemaking normoxia		Pacemaking hypoxia
Coronary blood flow (ml /100 ml /min)					
Mean	46 2		72 5		131 5
S D	12 7		18 9		60 0
p		<0 01		<0 01†	
Coronary vascular resistance $\frac{\text{mm Hg}}{\text{ml /100 ml /min}}$					
Mean	2 06		1 24		0 60
S D	0 62		0 32		0 30
p		<0 01		<0 01†	
Mean aortic blood pressure (mm Hg)					
Mean	89 0		85 3		64 4
S D	10 5		12 3		10 8
p*		>0 2		<0 01†	
Heart rate (beats/min)					
Mean	70 4		180		180
S D	22 0				

* Significance of the difference between the values of control and pacemaking under normoxia
† Significance of the difference between the values under normoxia and hypoxia at constant pacemaking
The p values were obtained using Student's paired t test

it caused no significant change in the mean aortic blood pressure Hypoxia significantly elevated the flow still further (p < 0 01) Since hypoxia caused a significant decrease in the mean aortic blood pressure (p < 0 01) as shown in Fig 2 *C* it became clear that hypoxia had a considerable effect on the reduction of the coronary vascular resistance as shown in Fig 2 *B* The serial measurements marked with asterisks were made after treatment with propranolol However the treatment seemed to cause no significant changes in the coronary vasodilatory effect of hypoxia The mean values standard deviations and p values of these variables are summarized in Table I

The effect of hypoxia on the coronary blood flow was observed in 7 dogs without pacemaking Since in this case the heart rate was not fixed at a constant level the heart rate was increased by hypoxia (p < 0 01) as summarized in Table II The control value for this test differed somewhat from those in Table I but the differences were not statistically significant The relationship between coronary blood flow and heart rate obtained for individual serial measurements is shown with closed circles connected with thick lines in Fig 3 *A* coronary blood flow being plotted on the ordinate versus heart rate plotted on the abscissa In the hypoxia test the mean aortic blood pressure also decreased Therefore the coronary vascular resistance decreased with increasing rapidity as shown in Fig 3 *B* where it was plotted against the heart rate For comparison with the hypoxia test the relationship between heart rate and coronary blood flow was studied in 8 serial measurements in 5 dogs with the O_2 at the air level In this experiment starting from slow spontaneous beating the heart rate was increased stepwise by electrical stimulation The results are

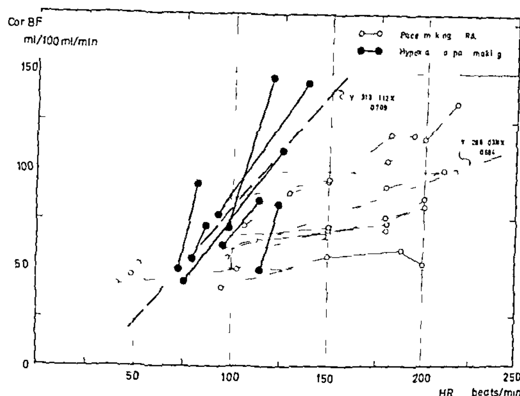


Fig. 3A. Relation between coronary blood flow and heart rate under two conditions—with pacemaking under room air (*RA*) breathing (open circles and thin lines) and without pacemaking with the gas for breathing changed from room air to hypoxia (closed circles and thick lines). The regression lines for each condition are indicated by the broken lines.

Table II. Hemodynamic values in seven dogs without pacemaking

Variables	Normoxia (control)	Hypoxia
Coronary blood flow ml/100 ml/min		
Mean	58.6	105.4
S.D.	12.0	23.6
p	<0.01	
Coronary vascular resistance $\frac{\text{mm Hg}}{\text{ml/100 ml/min}}$		
Mean	1.46	0.70
S.D.	0.42	0.17
p	<0.01	
Mean aortic blood pressure (mm Hg)		
Mean	82.4	69.3
S.D.	16.9	16.9
p	<0.01	
Heart rate (beats/min.)		
Mean	90.1	112.7
S.D.	14.8	20.9
p	<0.02	

shown by thin open circles together with those obtained in the hypoxia test without pacemaking (Figs. 3A and B). The values obtained for a given experimental series with each dog are connected with thin lines. These lines are clearly less steep than those in the hypoxia test without pacemaking. Furthermore, the mean gradient of the lines obtained for individual serial measurement was calculated—i.e., the rate of increase of coronary blood flow versus 10 beats per minute of heart rate. The values calculated are summarized in Table III both for the test with pacemaking under normoxia (left column) and for the hypoxia test where the inspired gas was changed from air to hypoxia (right column). According to Student's non paired t test the difference in the rate of increase was significant at the 1 per cent level.

A similar result was obtained also for the rate of decrease of coronary vascular resistance versus heart rate as shown in Table IV. These results suggest that the coronary vasodilatory effect of hypoxia was stronger than that due to the simple increase in heart rate.

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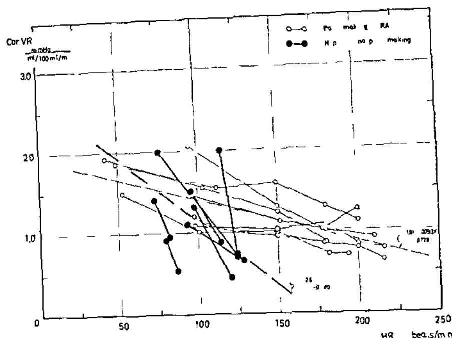


Fig 3B Relation between coronary vascular resistance and heart rate under the same two conditions as in Fig 3A

Table III *Rate of increase of coronary blood flow versus heart rate—* $\frac{ml/100\ ml/min}{10\ beats/min}$

Measurement no	Pacemaking under normoxia	No pacemaking change from normoxia to hypoxia
1	1 445	37 44
2	4 772	12 56
3	? 175	48 22
4	? 251	14 84
5	5 399	26 67
6	3 209	35 05
7	3 45?	13 76
Mean	3 243	26 93
SD	1 437	13 88
p	< 0 01	

The p l obt ned si g St d t no p red t test

Table IV *Rate of decrease of coronary vascular resistance versus heart rate—* $\frac{\frac{mm\ Hg}{ml/100\ ml/min}}{10\ beats/min}$

Measurement no	Pacemaking under normoxia	No pacemaking change from normoxia to hypoxia
1	0 0851	1 415
2	0 0519	0 350
3	0 0749	0 500
4	0 0446	0 100
5	0 0376	0 583
6	0 0459	0 386
7	0 0635	0 265
Mean	0 0576	0 513
SD	0 0174	0 425
p	< 0 02	

Th p al obtained si g St d t no p ed t t t

Discussion

When the heart rate was left uncontrolled it was increased by hypoxemia even in the reserpinized dogs Under such conditions the coronary vasodilatory effect of hypoxemia could not be distinguished from the effect of the increased heart rate on the coronary blood flow since tachycardia also caused an increase in coronary blood flow as shown in Fig 3 A So the heart rate must be kept constant at a rate of 180 beats per minute by use of a pacemaker

throughout both respiration in air and hypoxia. This rate of pacemaking was found to be suitable by trial and error experiments with three reserpinized dogs. The rate must be sufficiently higher than the spontaneous heart rate occurring under hypoxemia. But when the rate was excessive, the heart beat often became arrhythmic under hypoxemia.

From Fig. 2 and Table I it can be seen that even at a constant heart rate the coronary blood flow was significantly increased by hypoxemia when compared to the value under normoxemia. This result indicates that hypoxemia directly increased coronary blood flow independent of the heart rate. This was supported also by data concerning the relation between heart rate and coronary blood flow shown in Fig. 3. When the heart rate was increased under normoxemia by pacemaking, the coronary blood flow increased only slowly. However, when the heart rate was increased by hypoxia, the increase in coronary flow was more marked. Thus in Figs. 3,*A* and *B*, where coronary blood flow and vascular resistance are plotted against heart rate, two clearly different regression lines were obtained. When the increasing rate of coronary blood flow relative to that of the heart rate was calculated for these two different procedures, a statistically significant difference was obtained.

As another cause of the coronary vasodilatory effect of hypoxemia, the aortic blood pressure must be taken into account since it causes a proportional change in coronary blood flow.[12] However, since in reserpinized dogs the aortic blood pressure was significantly reduced by hypoxemia, the change in the aortic blood pressure acted rather to decrease the coronary blood flow. As seen in Fig. 2,*A*, the coronary vascular resistance was decreased strongly by hypoxemia. These results show that hypoxemia caused a stronger coronary vasodilation than that produced by the changes in heart rate and aortic blood pressure alone.

The treatment with reserpine exhausts catecholamines in tissues.[8,13] This was ascertained also in the present study using Weil-Malherbe's technique.[14] In two of the reserpinized dogs the concentration of norepinephrine in the left ventricular myocardium was measured and found to be 0.015 and 0.017 μg per kilogram of body weight, which was less than 1.5 per cent of the control values observed in two intact dogs. Moreover, epinephrine was undetectable. According to Wollenberger and Shahab,[15] catecholamines are released from the myocardium under anoxia. When an animal was pretreated with tyramine, even though this drug has only a weak depleting action on the catecholamines pooled in the tissue, these catecholamines were no longer released from the myocardium even under anoxia. On the other hand, it is said that hypoxia produces an increase in sensitivity of the sympathetic adrenergic receptors.[16] The release of newly formed catecholamines also could not be excluded in the reserpinized dogs. In an attempt to eliminate these conditions, two reserpinized dogs were further treated with propranolol. This treatment, however, seemed not to cause any significant changes in the coronary vasodilatory action of hypoxemia. Thus it is probable that the possible regulatory effect of intrinsic catecholamines on the coronary blood flow was at least largely reduced in the present reserpinized dogs and that the coronary vasodilation by hypoxemia was caused to a great extent through its direct metabolic action without the mediation of catecholamines.

The effect of metabolites such as CO_2, lactate, and pH have been studied by several previous workers.[17,18,19] They showed that these agents were of no importance as factors dilating the coronary vessels under physiological conditions. In 193? Rigler[9] suggested that adenosine derivatives released from the myocardium might regulate the coronary blood flow. Since then his hypothesis has been intensely studied in various ways. According to Katori and Berne,[4] adenosine can be found in the effluent perfusate flowing through the isolated anoxic heart. However, this has not yet been ascertained for the heart *in vivo* under normal physiological conditions. Thus the question as to whether the mechanism suggested by Katori and Berne is sufficient to explain the effect of hypoxemia remains unsolved. Moreover, Afonso[1] reported that lidoflazine, which inhibited decomposition of adenosine in blood, suppressed the coronary vasodilatory effect of hypoxia and tachycardia, and he further stated that the adenosine hy-

pothesis lacked concrete experimental support The mechanism of the metabolic regulation must be investigated further It at least appears probable that some metabolic mechanism participates in the coronary vasodilation by hypoxemia *in vivo* without the mediation of catecholamines

Summary

The present study was undertaken to investigate the direct coronary vasodilatory effect of hypoxemia independent of the intrinsic catecholamines The dogs employed were previously reserpinized and their heart rate was made constant at a rate of 180 beats per minute by an electrical pacemaker Under such conditions the coronary blood flow was determined during respiration both in air and in hypoxia by means of H_2 catheter electrodes placed in the aorta and coronary sinus respectively It has been shown that the coronary vascular resistance could be decreased significantly by hypoxemia even under such restricted conditions This observation suggested that hypoxemia dilated the coronary vessel to a great extent independent of the mediation of catecholamines A direct vasodilatory effect of hypoxemia was further supported by results concerning the relation between the coronary blood flow and heart rate When the heart rate was increased by pacemaking under normoxemia the coronary blood flow increased only slowly On the other hand when the heart rate was increased by hypoxemia the flow increased at a significantly more rapid rate than in the former instance This means that hypoxemia increased both the coronary blood flow and the heart rate but its primary effect on the coronary blood flow was stronger than the secondary effect caused by the change of heart rate in the reserpinized dogs

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Animal studies of effect of chronic exercise on the heart and atherosclerosis A review

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Exercise is being recommended as a preventive and therapeutic measure against atherosclerotic cardiovascular disease This concept is mainly based on the well documented hemodynamic changes secondary to physical conditioning[1, 2] and on certain epidemiological studies[3, 6] The hemodynamic changes are considered to reflect advantageous adaptations of the cardiovascular system and the epidemiological studies have been interpreted by some as demonstrating that exercise is important in the prevention of atherosclerosis However human studies regarding the actual morphological changes in the cardiovascular system are limited due to difficulties in controlling the many factors contributing to the atherosclerotic process the understandable reluctance to perform serial invasive procedures and time as well as expense limitations Also many investigators do not consider the epidemiology studies of physical inactivity as a risk factor for coronary artery disease to be conclusive[7, 9]

For these reasons, a careful review of the studies investigating the effects of exercise on the heart and the atherosclerotic process should be of importance in evaluation of the physical activity hypothesis Not all of the literature can be included in this paper, Table I lists the subjects covered

Myocardial hypertrophy

Numerous studies have demonstrated that vigorous exercise can produce cardiac hypertrophy in animals[10, 13, 21, 24, 31, 33, 35-41] Poupa and his colleagues[10] have reported that the heart/body ratios are invariably larger in the wild as compared to the domestic form of an animal species Bloor and associates[11] and Leon and Bloor[12] have presented data showing that the heart hypertrophies due to exercise in young rats whereas in the old rat exercise causes a decline in heart weight due to a loss of myocardial fibers or a decrease in fiber mass Tomanek and his co workers[13] have also demonstrated the age dependent hypertrophy response of the rat heart to exercise

Unfortunately the cellular morphological mechanism of exercise cardiac hypertrophy has not been determined There is even controversy regarding pathological cardiac hypertrophy, which has been investigated more extensively in animal experiments as reviewed by Meerson[14] In exercise hypertrophy the increased cardiac weight could

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be due to myocardial fiber hyperplasia fiber hypertrophy or both The classical belief has been that myocardial fiber hyper plasia does not occur beyond the immediate postnatal period However there are sev eral studies involving rat and human myo cardial tissue that support the concept that myocardial fiber hyperplasia occurs beyond this time[1 16] Also Laks and asso ciates[17 18] have demonstrated an increase in fiber length in biventricular hypertrophy in dogs secondary to pulmonary artery band ing

Hyperplasia and fiber lengthening which could result in increased cardiac mass with out fiber thickening are advantageous as compared to fiber thickening which occurs with pathological cardiac hypertrophy[18] Maintenance of normal fiber diameter is important since the diffusion distance from surrounding capillaries to central myofibrils is not increased The exercise study of Tomanek[20] showing constant myocardial fiber diameter favors hyperplasia and/or fiber lengthening as the cellular morpho logical mechanism of exercise cardiac hy pertrophy

Myocardial histological changes

Poupa and his colleagues have reported a number of interesting cardiac histological findings Table II summarizes their quan titative histological analysis of rat hearts at various ages and shows the effects of aging on the heart

Poupa in comparing tame to wild ani mals (tame rabbit to hare domesticated rat to wild rat etc) found that the density of muscle cells and capillaries is much greater in the more active wild animals In an experiment utilizing surgical constriction of the aorta he induced a 35 per cent in crease in heart weight in one month-old and in adult rabbits In the young rabbits the hypertrophied hearts showed a normal capillary density in the adult rabbits it was decreased From these observations Poupa hypothesized that in young animals cardiac hypertrophy is secondary to fiber hyperplasia while in older animals it is secondary to cellular hypertrophy Also he hypothesized that the capillary bed re ponds to growth stimuli most markedly if applied at an early age

Tomanek[20] studied the age related re sponse of the ventricular capillary bed and myocardial fiber width in male albino rats to chronic exercise Eighty male Sprague Dawley rats aged 40 days (young) 130 days (adult) or 575 days (old) were as signed to experimental or control groups The exercised rats ran on a treadmill 6 days a week for approximately 40 minutes for 12 weeks The rats developed a resting bradycardia with this exercise program At autopsy the myocardial fiber width was constant at about 12 microns while the capillary/fiber ratio increased in the exer cised rats over the controls in all age groups The capillary density decreased with age and was increased over the controls only in the young exercised rats

Leon and Bloor[11 12] have also performed rat experiments studying the effects of chronic exercise on the heart at different ages Male rats aged one to 12 months were divided into three age groups equivalent to the teen years the twenties to forties and the fifties to seventies in man Each of these age groups was subdivided into a control group a group that swam for one hour daily and a group that swam for an hour two days a week After ten weeks the ani mals were killed Table III summarizes those authors results and their explana tions for their findings They concluded that although the response of the rat heart to chronic exercise varies with age the capil lary/fiber ratio increases at all ages Their data regarding capillary changes are in agreement with the findings of Tomanek[20]

The only studies of the effects of an experimental program of exercise on myo cardial capillary density using a species

Table I Animal studies of the effects of chronic exercise subjects covered in this article

1 Myocardial hypertrophy
2 Myocardial histological changes
3 Coronary artery size changes
4 Coronary collateral circulation
5 Cardiac mechanical and metabolic performance
6 Skeletal muscle mitochondria and respiratory enzyme changes
7 Myocardial mitochondria and respiratory en zyme changes
8 Atherosclerosis and serum cholesterol

*Table II Histological changes in the hearts of nonexercised rats**

Age	*Capillaries (/mm²)*	*Muscle fibers (/mm²)*	*Capillary/muscle fiber ratio*	*Diffusion distance*	*Summary*
Birth to weaning	Increasing	Decreasing	Increasing from 0 25 to 1	Increasing	Number of capillaries muscle cells and cell diameters increasing
One to two months of age	Increasing	Increasing	1 1	*Increasing*	*Capillary growth stops no* change *in* number of *muscle* fibers but fibers *increase in* diameter
Adults	Decreasing	Decreasing	1 1	Increasing	Capillary growth stops no change *in number of muscle* fibers but fibers *increase in* diameter
Old (72 mo)	Decreasing	No change	Decreasing	Increasing	Loss of capillaries

*Summarized from Poupa O Rakusan K and Ostadal B The effect of physical activity upon the heart of vertebrates Medicine and Sport 4 202 1970

*Table III Summary of rat exercise study of Leon and Bloor**

Age	*Sarcoplasm mass*	*Capillary number and density*	*Capillary/ fiber ratio*	*Heart/body ratio*	*Coronary artery luminal area*
Young	Increased due to fiber hyperplasia and hypertrophy	Increased	Increased due to capillary proliferation	Increased	Increased
Adult	Increased probably due to increased fiber size	No change	Increased	Increased only in daily exercised group	Increased only in daily exercised group
Old	Decreased	No change	Increased due to loss or decreased size of fibers	No change	No change

*Summarized from Leon A S and Bloor C M Exercise effects on the heart at different ages (abst) Circulation 41 and 42 (Suppl III) 50 1970 Reproduced by permission of The American Heart Association Inc

other than the rat have been those of Petren and associates [1] and Hakkila [2] Both used guinea pigs Petren s data showed an increase in capillary density whereas Hakkila found a decrease

Coronary artery size changes

Tepperman and Pearlman[23] studied the effects of exercise on the coronary tree of rats by the corrosion cast technique One group of rats ran approximately one mile a day for 36 days while another group swam for 30 minutes a day for 10 weeks When the animals were killed their hearts were weighed and then the coronary arteries were injected with vinyl acetate The hearts were digested with potassium hydroxide, and then the casts of the coronary arteries were weighed alone Compared to the controls both groups had an increased heart/body weight ratio and an increased coronary tree cast weight/heart weight ratio

Stevenson and co workers [4] used the same corrosion cast technique to ascertain the effects of exercise of different types frequency and duration Table IV summarizes their results Their conclusion was that in the rat forced exercise caused an increase in the coronary tree size as compared to the cardiac weight provided the exercise was not too strenuous or frequent

As mentioned before the study of Leon

*Table IV Summary of rat heart corrosion cast exercise study of Stevenson and associates**

	Heart to body weight ratio	Coronary cast weight to heart weight ratio
Treadmill exercise (1.3 Km /day)		
I Control	0 35	1 7
II ? times a week for 4 weeks	0 31	2 7
III 5 days a week for 2 weeks then none for 2 weeks	0 34	? 5
IV 5 days a week for 4 weeks	0 38	1 9
Moderate swimming exercise		
I Controls	0 40	2 31
II Constant swimming 60 min 5 day /week for 1 month	0 41	3 0
III Intermittent swimming 60 min 5 days/week for 1 month	0 43	2 9
IV Constant swimming 60 min 2 days/week for 1 month	0 44	3 0
Continuous severe swimming exercise		
I Controls	0 36	2 9
II 1 hour/day 4 days/week for 1 month	0 38	3 2
III 2 hours/day 4 days/week for 1 month	0 40	3 7
IV 4 hours/day 4 days/week for 1 month	0 42	3 3

*St so J A F l k V Rech t P et l Effect f e se co ry t ee in th t C R s. 15-65 1964 R p o-
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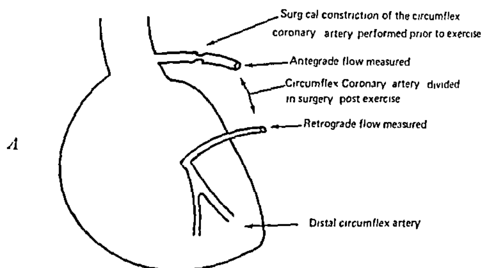
and Bloor demonstrated that swimming exercise in rats resulted in an increased luminal cross sectional area of the main coronary arteries in the animals that experienced an increase in ventricular weight that is only the young and strenuously exercised adult rats These results are supported by the studies of Kerr and colleagues that demonstrated coronary artery enlargement in rats with cardiac hypertrophy induced by hypoxia aortic constriction and thyroxin Also it has been shown that the relationship between total heart weight and the diameter of the coronary arteries and ostia are linear in man up to the upper weight limit of physiological hypertrophy [26]

Coronary collateral circulation

Eckstein[27] has reported a study on the effect of exercise and coronary artery narrowing on coronary collateral circulation (see Fig 1) He surgically induced a constriction in the circumflex artery of approximately 100 dogs Various degrees of narrowing were induced but only dogs that developed electrocardiographic changes were included in the study After one week of rest the dogs were divided into two groups One group was exercised on a tread mill one hour a day five days a week for six to eight weeks The other group remained at rest in cages The extent of arterial anastomoses to the circumflex artery was then determined as follows The animals were anesthetized a second thoracotomy was performed and their blood pressure was stabilized mechanically The circumflex artery was isolated and divided beyond the surgical constriction The flow rate through the constriction and the flow rate from the distal end of the artery were measured The flow rate through the constriction was considered to be inversely related to the degree of constriction

When these values were plotted against one another it was shown that the less the antegrade flow or the greater the constriction the greater the retrograde or collateral flow Also the exercised dogs had a greater value for retrograde flow than the rested dogs for any degree of constriction Eckstein concluded that moderate and severe arterial narrowing results in collateral development proportional to the degree of narrowing and that exercise leads to even greater coronary anastomosis

Burt and Jackson[28] used similar methods



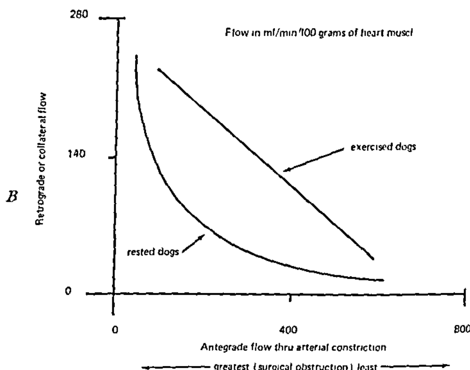


Fig. 7. A and B. Eckstein's dog study of the effects of coronary artery constriction and exercise on collateral flow. (Modified from Eckstein, R. W.: Effect of exercise and coronary artery narrowing on coronary collateral circulation. Circ. Res. 5:230, 1957. Reproduced by permission of The American Heart Association, Inc.)

to study the effects of exercise on the collateral vessels of "normal" dogs. Twenty dogs were used, 13 rested and seven exercised. Prior constriction of a coronary artery was not performed as in Eckstein's experiment. After one month of treadmill exercise, surgery was performed and retrograde flow measured from the distal portion of the circumflex artery with its proximal end ligated. There was no difference found in retrograde flow between the two groups. The authors concluded that exercise alone in normal subjects or in the absence of an ischemic lesion is not sufficient to stimulate coronary collateral growth.

Kaplinsky and co-workers[29] studied the effects of physical training in dogs after coronary artery ligation. Forty dogs were surgically subjected to complete occlusion of the left anterior descending coronary artery. Twenty-six dogs survived and after one week of rest were divided into an exercise and a control group. The exercised dogs were run on a treadmill for an hour six days a week for five weeks, and then both groups were put to death. A training effect was demonstrated in the exercise group. Selective cineangiography and postmortem coronary injections demonstrated extensive collateral formation but there was

no difference between the two groups The authors concluded that exercise may not enhance collateralization when a large vessel is totally occluded

Cobb and associates[20] studied the effects of exercise on acute coronary occlusion in dogs with a prior partial occlusion The anterior descending coronary artery was partially occluded (35 to 70 per cent) in 50 dogs and then they were divided into a control and an exercise group The exercise consisted of treadmill running for 40 minutes a day for three months Following this a complete occlusion of the anterior descending artery was surgically produced The animals were monitored for arrhythmias for six days then sacrificed and their hearts removed The coronary vessels were injected and the collateral vessels quantitated radiographically The two groups did not differ as to the extent of the infarct relative to the partial occlusion the frequency of arrhythmias or the extent of radiographically quantitated collaterals

Cardiac mechanical and metabolic performance

Penpargkul and Scheuer[21] have reported the effect of physical training on the mechanical and metabolic performance of the isolated rat heart Rats were exercised by swimming for 2½ hours a day five days a week for two months The exercised rats and controls were killed and their hearts isolated in a perfusion apparatus with cannulas inserted for life support pressure and flow measurement and metabolic analysis When compared with sedentary controls the hearts from conditioned rats had higher levels of cardiac work and output Atrial pacing at increased rates caused greater differences in these parameters and left ventricular pressures and dp/dt became higher in conditioned hearts Atrial pacing also resulted in greater O_2 consumption in conditioned hearts whereas higher lactate and pyruvate concentrations occurred in sedentary hearts Raising atrial filling pressures resulted in ventricular function curves which were superior in the conditioned hearts Also there were greater increments in O_2 consumption a higher aerobic/anaerobic energy production ratio and increased coronary artery flow The authors concluded that in physically trained rats the function of the heart as a pump is improved and that this is at least partially due to improved O_2 delivery

Crews and Aldinger[3] have also presented data to support the concept that the exercise hypertrophied heart is functionally superior to the normal heart They randomly divided 30 female rats into control and exercise groups of 15 each The exercised rats swam for six hours a day for approximately one month Then a thoracotomy was performed and isometric systolic tension was measured while the animals were physiologically supported This measurement is felt by the authors to reflect potential contractility and cardiac work Measurements were also made of left ventricular pressure before and during aortic constriction The animals were sacrificed and body weight ventricular thickness cardiac weight and cardiac volume determined All of these parameters were significantly increased in the exercise group as compared to the controls The authors concluded that exercise cardiomegaly is advantageous in the maintenance of homeostasis during exercise Aldinger[22] has reported a similar study involving a control and exercised group of rats receiving digitoxin This study demonstrated that unlike the pathological hypertrophy of disease exercise hypertrophy and the increment in myocardial function concomitant to the hypertrophy are not altered by digitoxin

Skeletal muscle mitochondria and respiratory enzyme changes

The changes that occur in chronically exercised skeletal muscles have been confirmed by numerous investigators as reviewed by Holloszy[24] Mitochondria are increased in number size and the number of cristae Amounts of mitochondrial protein and respiratory enzymes are increased per gram of fresh muscle There is an increased capacity for adenosine triphosphate (ATP) production and aerobic metabolism of many substrates Myoglobin concentration is increased This adaptation must partially account for the increased aerobic work capacity[25] and for the decreased muscle blood flow at any level of submaximal exercise[26,27] that occurs secondary to physical conditioning

Myocardial mitochondria and respiratory enzyme changes

Arcos[38] and his colleagues studied female rats using a protocol similar to that used by Aldinger. The rats were separated into a control group and into three swimming groups with total swimming time ranging from 60 to 500 hours. The rats who exceeded 300 hours of total swimming could not continue swimming six hours a day and so their daily time had to be decreased. The rats were sacrificed and their hearts analyzed by various methods. Mitochondrial mass was increased only in the rats that swam for approximately 160 hours. Electron microscopy showed increased size and number of mitochondria in this group while mitochondrial degeneration was noted in rats exercised for a longer time. No change in the respiratory rate of myocardial homogenates was found between the groups. The microscopic and histochemical sections showed evidence of myocardial degeneration in the exercised rat hearts. The authors suggest that the increase in mitochondrial mass is a compensatory response to exercise and this increase brings about focal regions of hypoxia during overexercise responsible for degenerative changes.

Aldinger and Sohal[39] repeated the previous experiment but with the total swimming time increased to between 400 and 1,500 hours. Also, a control and an exercise group treated with digitoxin were included. Again, mitochondrial degenerative changes were seen in the myocardium of the nontreated swimmers; however, the swimmers receiving digitoxin showed no degenerative changes. In fact, they had an increase in the size of the mitochondria and in the number of mitochondrial cristae. In addition, the following subcellular changes occurred in the myocardium of both swimming groups: (1) increased mitochondrial/myofibril ratio, (2) occasional areas of myocardial hemorrhage, (3) increased distance between nuclei, and (4) dilatation and vesicle formation within intercalated discs. The authors suggested that some of these changes did not appear beneficial but concluded that the morphological integrity of the myocardial mitochondria is better preserved in the swimming rat receiving digitoxin than in the untreated swimming rat.

Banister, Tomanek and Cvorkov[40] have reported a study of the effects of chronic exercise on rat heart mitochondrial morphology using the electron microscope. Male rats were run to exhaustion on a motor-driven treadmill for one hour a day over a 65 day period. Throughout the training period four animals were sacrificed on certain days. The four consisted of one control, one trained animal killed immediately after exercise, one killed 30 minutes after exercise, and one killed 24 hours after exercise. On the first training day, exhaustive running resulted in mitochondrial degeneration in animals killed immediately and 30 minutes after exercise. The rat killed 24 hours after exercise showed mitochondrial morphology similar to the unexercised control rat. The effects of training began to appear after ten days of training. Fewer altered mitochondria were seen in the trained rats sacrificed at any period after exercise. This study demonstrates that with physical training exhaustive exercise has a less damaging effect on myocardial mitochondria, suggesting that this organelle adapts to exercise.

Oscai, Mole and Holloszy[41,42] have studied rats using various exercise protocols including the same swimming protocol used by Arcos and Aldinger. They could not confirm an increase in mitochondrial protein or respiratory enzymes in the myocardium of exercised rats. They suggested that the capacity for aerobic metabolism of normal untrained rat myocardium is adequate to meet the increased demands for ATP imposed by an exercise program without increasing mitochondrial mass or respiratory capacity. They found that respiratory enzyme levels are approximately five times higher in the heart than in the gastrocnemius muscle of the sedentary rat. They confirmed the interesting finding that exercise depresses the appetite of male rats while it does not affect the appetite of female rats. Because of problems with growth differences secondary to this phenomenon between controls and exercised rats, some investigators have used only female rats.

Scheuer and co-workers[43] have measured increased cardiac glycogen stores in conditioned rat hearts but found no increase in

the concentration of high energy phosphate compounds

Atherosclerosis and serum cholesterol

McAllister and colleagues[44] have reported an experiment that demonstrated an accelerating effect of muscular exercise on experimental atherosclerosis Ten mongrel dogs were placed on identical high cholesterol diets of equal caloric value and 150 mg of thiouracil daily The diet and thyroid antagonist were used to shorten the time period of the study The dogs were treated identically except that five were trained to run five miles a day at five miles per hour on a treadmill At the end of one year angiograms were performed then the dogs were sacrificed and their arteries analyzed for the extent of atherosclerosis During the course of the study period the serum cholesterols progressively rose with the runners having higher values The runners also showed more atherosclerosis than the sedentary dogs in all vessels including the coronaries

Myasnikov[4] reported the results of studies performed by himself and his colleagues in Russia Ten rabbits were given a high cholesterol diet 25 rabbits received the same diet but were run to exhaustion daily on an electric treadmill and eight rabbits received no cholesterol but were exercised The exercised rabbits on a high cholesterol diet had lower serum cholesterols than those not exercised At the end of six months the animals were sacrificed and visual estimation showed that the physical exercise reduced to some extent the development of atherosclerosis in the aorta and coronary arteries However for unknown reasons there were more marked pathological changes in the myocardium of the exercised rabbits receiving cholesterol than in either of the other groups

Kobernick and his co workers[46] reported the results of a similar study Eighteen rabbits were fed high cholesterol diets and exercised ten minutes a day while a non exercised matched group received the same diet Serial serum cholesterol values did not differ between the groups After 13 weeks the rabbits were sacrificed and their aortas inspected visually for atherosclerosis and chemically analyzed for cholesterol The exercised rabbits had greater muscle mass less body fat deposits and less aortic atherosclerotic involvement than the non exercised rabbits

Warnock and colleagues[47] reported an exercise study using young male roosters All of the birds were caged and fed an atherogenic diet Ten remained caged while 14 were taken from the cage and forced to walk briskly for one hour a day (approximately four miles a week) Weekly serum cholesterol values were determined and found to be lower in the exercised birds The food consumption was equal in both groups but the exercised birds were heavier At the end of fourteen weeks the birds were sacrificed and the aorta its main branches and samples of brain and liver were assayed for cholesterol The cholesterol content was lower in the assayed vessels and liver of the exercised birds than in the nonexercised birds The coronary arteries were not studied

Carlson[48] has reported the results of strenuous exercise on the serum cholesterol of old rats The trained group ran three hours daily for one month At the end of this period the serum cholesterol averaged 186 mg per cent in the trained group and 250 mg per cent in controls The extent of atherosclerotic involvement was not studied Faris and his co workers[49] performed a similar study in young rats Both the control and exercised animals had serum cholesterol readings of about 45 mg per cent and there was no statistical difference between the groups Neither investigator discussed the diet fed their rats but Carlson stated that lipid levels in rats increase with age as they do in man

Conclusions

If the effects of chronic exercise in animals are similar to the effects in man then the animal studies demonstrate concepts applicable to the preventive and therapeutic use of physical conditioning in atherosclerotic cardiovascular disease Human studies will be referred to that support the concepts learned from the animal studies

In young rats myocardial fiber mass contractility and capillary/fiber ratio as

well as coronary artery size can be increased by regular strenuous exercise. In older rats, exercise can improve myocardial perfusion by relatively increasing the capillary/fiber ratio. The other changes do not occur in older rats and contractility has been studied only in young rats. The applicability of these findings to man is supported by autopsy studies demonstrating myocardial hypertrophy and concomitant coronary artery enlargement in athletes and manual laborers.[26,50,51] Increased myocardial contractility is suggested by the improved hemodynamic response to exercise secondary to physical conditioning programs that occur in both young[52,53] and older[54,55] subjects, although other factors are also involved in these changes.[36,37,56,57] The age-dependent response of the rat heart is paralleled by the decreased training response in older subjects.[55] If these adaptations are advantageous, then exercise programs should begin in childhood because of the greater cardiac response to training.

The studies regarding collateral vessel formation are contradictory, but the study of Eckstein is technically superior. His findings support the concept that exercise adds to the effect of ischemia in opening collateral coronary vessels. The opposing results in the two other studies suggest that the radiographic quantitation of collaterals is not as sensitive as the backflow method used by Eckstein. Burt and Jackson's study, which did not demonstrate an increase in collateral coronary flow in normal subjects, is provocative but requires confirmation. Unfortunately, there are no controlled human studies of the influence of exercise on coronary collaterals or collateral flow.

The intact[32] rat heart and isolated[31] rat heart studies demonstrate that the exercise-hypertrophied heart is functionally superior to the normal heart. However, the increase in rat skeletal muscle mitochondria and respiratory enzymes must partially account for the increased aerobic work capacity[35] and for the decreased muscle blood flow at any level of submaximal exercise[36,37] that occurs secondary to physical conditioning. These morphological and metabolic findings in skeletal muscle have been confirmed in human subjects.[59,60]

The myocardial electron microscopy studies demonstrate that chronic exercise protects the morphology of the mitochondria from exercise stress, suggesting that their function and that aerobic metabolism are better maintained. The influence of digitoxin in this regard is interesting. The reported hemorrhagic areas and intercalated disc changes in the hearts of rats subjected to prolonged intermittent exercise suggest a harmful effect of severe chronic exercise. The controversy as to whether myocardial mitochondria or respiratory enzymes increase as a result of chronic exercise should be settled by further investigations.

The animal studies regarding the effect of chronic exercise on atherosclerosis are suggestive of a protective influence but are not conclusive, especially as concerns the coronary arteries. Autopsy studies have failed to detect any difference in the extent of atherosclerosis in individuals who were in sedentary or active occupations prior to death.[61,63] Definitive animal studies are needed.

As in these animal studies, the results of studies regarding the effects of chronic exercise on serum cholesterol in man are inconclusive and contradictory. The human studies have recently been reviewed by Gustafson.[64] It appears that regular exercise can lower cholesterol levels somewhat, but that diet, certain medical disorders, and genetic differences are more influential.

Summary

Animal studies add considerable data to our knowledge of the effects of chronic exercise on the heart. They demonstrate that there are morphological and metabolic changes that make the cardiovascular system better able to withstand any stress, possibly even that imposed by atherosclerosis. These favorable adaptations are more marked in young animals than in older animals. However, the data regarding a beneficial effect of chronic exercise on the atherosclerotic process or on serum cholesterol levels are only suggestive and better studies are required to confirm this effect. Thus, the therapeutic and preventive use of exercise is supported by the animal studies, but these efforts should be adjunctive to modification of the risk factors that have a

well demonstrated influence on the athero sclerotic process [6, 67]

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The cause of luminal narrowing in internal mammary arteries implanted into canine myocardium

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Intimal proliferation has been implicated as a limiting factor in blood flow through internal mammary arteries implanted into myocardium. The cause of the proliferation is uncertain. This report summarizes observations from histologic examination of internal mammary arterial implants into canine myocardium, and provides evidence that thrombosis is the cause of the luminal narrowing.

Materials and methods

Bilateral internal mammary arterial implants were examined at necropsy in 6 mongrel dogs. In each animal one artery had been implanted deeply (average 8.9 ± 2.0 mm [mean ± S.D.]) into the left ventricular myocardium and the other one superficially (2.4 ± 0.7 mm) into the subepicardial muscle (Figs. 1 and 2). Each mammary artery had been dissected from its origin from the subclavian artery to its epigastric bifurcation. No side holes had been made in it, and its distal branches were left patent. Each artery had been implanted over a length of 4 to 5 cm in the left ventricular wall. The right internal mammary artery had been implanted

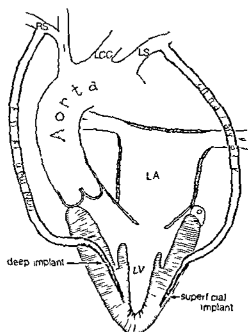


Fig. 1. Diagram of left side of heart and ascending and transverse aorta illustrating the manner in which the internal mammary arteries were implanted into the left ventricular (*LV*) wall. *I* = innominate artery; *LA* = left atrium; *LCC* = left common carotid artery; *LS* = left subclavian artery; and *RS* = right subclavian artery.

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Fig. 2 Photomicrograph of transverse section of canine left ventricle showing location of the superficial (S) and deep (D) internal mammary implants (Elastic tissue stain ×3)

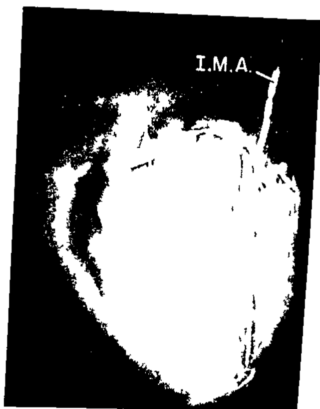


Fig 3 Postmortem radiograph of heart taken after injection of contrast material into the internal mammary artery (I M A) implanted into left ventricle The lumen of the implanted artery is severely narrowed near the left ventricular apex The left coronary artery is opacified by retrograde filling from the implanted internal mammary artery

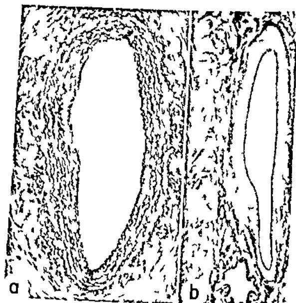


Fig 4 Normal canine internal mammary artery (a) and normal coronary artery (b) The mammary is an elastic artery and the coronary a muscular artery (Elastic tissue stains a ×40 b ×35)

anterolaterally and the left posterolaterally The sequence of the depth of implantation of the arteries had been alternated for the right and left sides Ameroid constrictors had been applied to the anterior descending and circumflex coronary arteries in one dog The coronary arteries of the other 5 animals were not altered

Seventeen months (506 ± 4 days) after mammary arterial implantation the dogs were studied hemodynamically [1] There after each was put to death and post mortem angiograms were performed after separate injection of contrast material into each of the implanted mammary arteries The hearts and internal mammary arteries then were fixed in 10 per cent buffered formalin After fixation each 4 to 5 cm segment of implanted mammary artery into myocardium was cut processed em

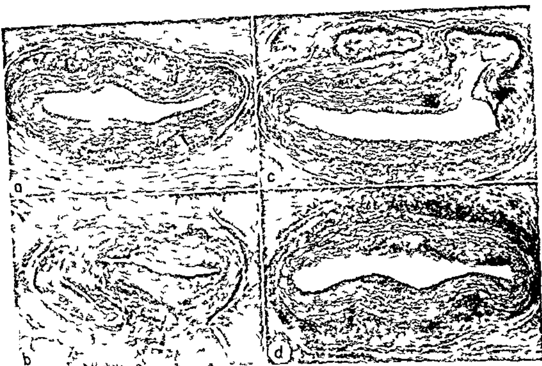


Fig 5 Implanted internal mammary arteries in a dog in which the anterior descending and left circumflex coronary arteries had been narrowed by an Ameroid constrictor before implantation. *a* Superficial implanted artery proximally *b* Superficial implanted artery distally At this point the lumen is considerably narrowed by fibrous tissue devoid of elastic fibrils *c* Deep implanted artery proximally A small branch which shows mild intimal thickening is arising at this point *d* Deep implanted artery distally Only mild intimal proliferation is present (Elastic tissue stains *a* ×50 *b* and *c* ×45 and *d* ×60)

bedded and sectioned at 6 micron intervals Every even tenth section was stained by hematoxylin and eosin and every odd tenth section by Verhoeff-van Gieson

Results

Postmortem angiograms disclosed evidence of terminal narrowing in each of the 12 implanted mammary arteries Nevertheless retrograde filling of the coronary arteries occurred after injection of contrast material into each of the implanted mammary arteries (Fig 3)

Both gross and histologic examination of each implanted mammary artery (elastic arteries in contrast to coronary arteries which are muscular arteries [Fig 4]) showed varying degrees of luminal narrowing The narrowing was least severe in the two internal mammary arteries implanted into the dog in which the left coronary arteries had previously been narrowed by Ameroid constrictors (Fig 5) The luminal narrowing of the implanted internal mammary arteries consisted of fibrous tissue containing generally numerous elastic fibrils but no lipid deposits cholesterol clefts or calcific deposits (Figs 6 to 9) Although some degree of intimal fibrous proliferation occurred along the entire length of the intramyocardial implants the severest degrees of narrowing occurred at the most distal portions of the implants (Figs 6 to 9) No fibrin or platelet aggregates were found in the lumens of any implanted mammary artery In several implanted arteries multiple luminal channels were present (Fig 9) The media of all implanted arteries appeared normal but usually the adventitia was obscured by dense fibrous tissue which was devoid of elastic fibrils

Comments

Intimal thickening develops within a short period in any internal mammary artery implanted into the myocardium[2,7] When this artery is implanted into the ischemic myocardium less intimal thicken

Fig. 6. Implanted internal mammary arteries in another dog. *a,* Proximal superficial implant showing only mild intimal thickening. *b,* Distal superficial implant showing severe intimal thickening by fibroelastic tissue. *c,* Proximal deep implant. The thin band of thickened intima partially dislodged. The disruption probably occurred at the time of arteriography. *d,* Distal deep implant showing severe intimal thickening by fibroelastic tissue. Generally, the degree of intimal thickening was similar in both superficial and deep implant. (Elastic tissue stains, each ×40.)

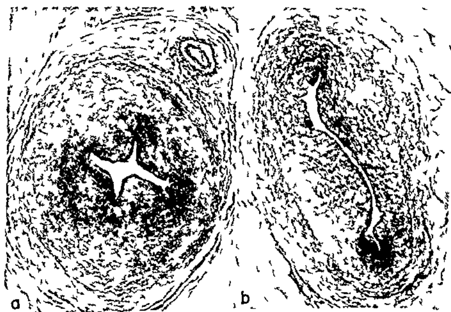


Fig. 7. Distal superficial (*a*) and deep (*b*) internal mammary implants in another dog. Each shows severe degrees of intimal thickening by fibrous tissue containing many elastic fibril. (Elastic tissue stains, each ×40.)

...ning occurs than when it is implanted into nonischemic myocardium[7] The cause of the intimal thickening has been uncertain Degeneration of the internal mammary artery itself due to lack of nutrition to its wall trauma to the artery inflicted either at the time of implantation or by effects of ventricular contraction or dilatation and thrombosis have been suggested as possible causes

The present study provides evidence that the cause of the intimal proliferation in the implanted arteries is in situ thrombosis The major evidence supporting organization of thrombi as the cause is the finding of multiple vascular channels within the intimal connective tissue (Fig 9) Multiple luminal channels in arteries have long been recognized as the hallmark of organization of thrombi[8] (Fig 10) The connective tissue in the lumens of the implanted internal mammary arteries with multiple luminal channels is similar to that in the vessels containing only one vascular channel which suggests that the cause of each is similar No fibrin or platelet aggregates known components of thrombi were observed in the implanted internal mammary arteries but the 17 month interval between implantation and death of the animals provided more than enough time for organization into fibrous tissue Actually it would be surprising if thrombus did not form in the distal portions of the tunnelled internal mammary arteries since flow of blood at these sites at least initially is considerably slowed Also after induced myocardial infarction in the dog marked reduction of flow in the anatomically patent coronary artery supplying the area of infarction occurs and this relative stasis may be responsible for thrombus formation in this vessel[9] Injection of either fibrin or whole blood clots into systemic veins of rabbits also produces fibrous tissue within the pulmonary arteries similar to that observed in the internal mammary arteries implanted into the canine myocardium[10]

Vachlas and associates[11] demonstrated that carotid arteries of dogs remained patent if implanted into the left ventricular myocardium and allowed to drain into the right ventricular cavity Arteries implanted into the left ventricular myocardium however without distal egress or ones that had



Fig 8 Distal deep internal mammary implant in another dog The lumen is severely narrowed peripherally by fibroelastic tissue but centrally by fibrous tissue devoid of elastic fibrils The lumen of the small branch also is narrowed by fibrous tissue containing few elastic fibrils (Elastic tissue stain ×40)

the distal lumen obstructed became occluded and developed intimal thickening These authors concluded that intimal thickening did not develop from trauma by the contracting myocardium but from a lack of continuous blood flow through the vessel From these reported findings plus the recanalization in the implanted arteries in the present experiments and others[6] it would appear that stasis of blood in the implanted artery proceeds to thrombosis with later organization

Summary

Attention is called to the cause of intimal thickening observed in the internal mammary arteries implanted in the myocardiums of 6 dogs Each of the 12 implanted arteries showed varying degrees of fibrous intimal thickening and several contained numerous channels The multiple luminal channels strongly suggest that the intimal thickening was the result of organization of thrombi The intimal thickening was less in the one animal in which the left coronary artery had been constricted before internal mammary artery implantation



Fig 9 Intimal fibrous thickening in a deeply implanted internal mammary artery in another dog a Proximally Here the luminal narrowing is caused primarily by fibrous tissue containing no elastic fibril although the cap over this fibrous tissue contains numerous elastic fibril b Distally The lumen at this point is occluded except for channels (arrows) The presence of the multiple channels strongly suggests that the intimal thickening resulted from organization of a thrombus (Elastic tissue stains a X42 b X40)

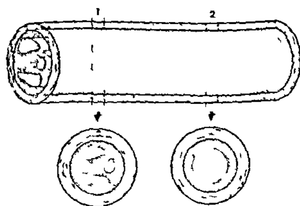


Fig 10 The multi and unichanneled artery Duguid[12] when studying coronary arterial serial sections of an organized thrombus noted that the tissue present between channels was similar to that found in arteries with only one channel Since the multichannel artery had been recognized as the hallmark of an organized thrombus and since the tissue in both multi and unichanneled arteries was similar he reasoned that the causative process also was similar

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Experimental Luciani-Wenckebach phenomenon in the anterior and posterior divisions of the left bundle branch of the canine heart

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The existence of Mobitz Type I block in the A-V junctional tissues has been demonstrated by clinical electrocardiography.[1] Scherf and Shookhoff[2] reproduced such phenomenon experimentally in both bundle branches of the canine heart more than forty years ago. Recently electrophysiological evidence of this entity was demonstrated on isolated preparations of the canine conducting tissue in the His bundle (HB)[3] and its branches.[4] The possibility that some intermittent bundle branch blocks (IBBB) could be attributed to progressive prolongation of the intraventricular conduction time has been confirmed in the human heart by Rosenbaum and associates[5] and Friedberg and Shamroth[6] in the right and left bundle branches (RBB, LBB) and Cerqueira Gomes and Visconcelos Teixera in the posterior division of the LBB.

In this report, accepting the anatomic trifascicularity of the intraventricular conduction system in most mammals[8,9,10] (Fig. 1), we demonstrate in the course of our experiments the existence of Wenckebach periods in the anterior and posterior divisions of the canine LBB.

Material and methods

Thirty mongrel dogs which weighed 10 to 15 kilograms were anesthetized with intravenous or intraperitoneal sodium pentobarbital. Intubation was performed for artificial respiration; the right vagus was isolated and sectioned and its distal part was connected to an electrical stimulator. Then the right femoral vein was exposed and a bipolar electrode catheter with an interelectrode distance of 4 mm. was introduced through it and placed under fluoroscopic and ECG control into the right ventricle. The catheter was then slowly withdrawn until its tip was in contact with the anterior part of the septal tricuspid valve leaflet till a biphasic spike measuring 20 msec. was obtained. This deflection appeared between the atrial and ventricular electrograms within the P-R interval of the standard ECG lead used as a reference, corresponding to the His bundle electrogram (HBE)[11] (Fig. 2). A thoracotomy without costal resection at the level of the right fourth intercostal space was performed and a limited pericardiectomy was made. With the idea of obtaining a similar

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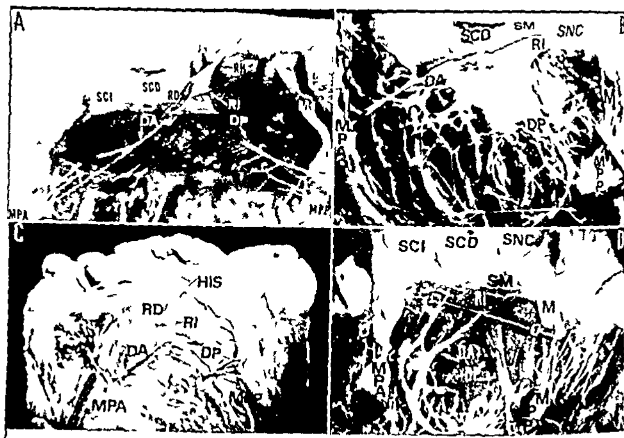


Fig. 1. *A* through *D*. Dissection of the main trunk and both divisions of the left bundle branch. Panel *A*, dog; Panel *B*, calf; Panel *C*, sheep; Panel *D*, human. *SCI* = left coronary sinus; *SCD* = right coronary sinus; *SNC* = non coronary sinus; *SM* = membranous septum; *M* = mitral valve; *RH* = His branching portion; *RD* = right bundle branch; *RI* = left bundle branch; *DA* = anterior division; *DP* = posterior division; *MPA* = anterior papillary muscle; *MPP* = posterior papillary muscle.

anatomical position as in the human specimen, we then proceeded to place the canine heart in the horizontal position stretching the cardiophrenic ligaments with a tube until the point of the heart had passed through a 45 degree angle upwards to the left. Later, a transmural puncture in the apex of the left ventricle was done; an electrode similar to the one described was inserted and directed to the outflow tract of this ventricle between the posterior and the two anterior thirds of the septum until the aortic valve was passed. Then it was withdrawn till the protuberance of the aortic cusp was perceived. At this level the distal electrode was between the right and non coronary sinus, under the *membranous septum* zone from where the LBB emerges. A biphasic deflection previous to the ventricular electrogram measuring 15 msec. was recorded; it corresponds to the LBB electrogram (LBE)[12] (see Fig. 3).

In seven *dogs* a bipolar catheter was inserted through the right primitive carotid artery under fluoroscopic control until the electrodes were positioned below the aortic valve to the highest part of the interventricular septum (Fig. 4). From this point an LBE could also be obtained[13] simultaneously with the HBE recorded from the right side of the heart (Fig. 3).

All records were made on a multichannel oscilloscope photographic recorder at a paper speed of 100 mm. per second. The filter frequencies of the ECG preamplifier were set at 40 to 150 cps. Right atrial pacing was performed with Medtronic equipment 5837.

Techniques to interrupt the RBB and to contuse both divisions of the LBB. An atraumatic needle with a blunt end was used. To interrupt the RBB the anterior papillary muscle was localized by palpation, then the right ventricle was punctured 0.5 cm. above it and the needle was directed to the convergence of the posterior wall of

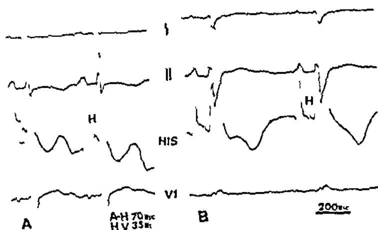


Fig 2 A and B A Normal ECG B RBBB produced experimentally in the same animal (see text)

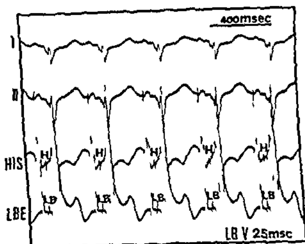


Fig 3 Simultaneous recording of His and LBB electrograms (see text)

the ventricle with the interventricular septum keeping in touch with the latter At this point a cut was made perpendicular to the septum producing an interruption of the RBB on its subendocardiac portion

To contuse the divisions a needle was inserted in the lateral wall of the left ventricle 1 cm above the apex Once into the ventricular cavity the needle was directed to the outflow tract until the aortic valve was passed then it was withdrawn till the rebound of the aortic cusp was perceived From now on the technique depended on which divisions had been chosen to be contused With the interior one a contusion parallel to the septum was performed on its anterior third for the posterior division a longitudinal contusion directed from the posterior leaflet of the mitral valve in its caudal insertion up to the apex of the left ventricle was done

For obtaining Wenckebach periods on the divisions a definitive interruption of the RBB was carried out and afterwards according to the chosen division of the LBB one was contused and a section was done on the other one Then a transitory trifascicular complete A V block could be obtained (Fig 5) In this illustration we see that the increase in the LB V time by 15 msec in the third H wave and the absence of the deflection of the LBE in the fifth and seventh auricular beats are due to the depolarization of the conduction tissue local



Fig. 4. Anteroposterior projection where the electrode catheters are observed. *A* = passing arterially to just beyond the aortic valve. *V* = reaching intravenously to the right intraventricular cavity.

ized above the recording site caused by concealed retrograde conduction from the previous idioventricular beat. The variations of the interval A I B depend on the magnitude of the coupling between the P wave and the preceding idioventricular beat determining that the stimulus reaches the transmembrane potential of the depolarized fibers during their refractory periods at different levels of repolarization.

When the contused division recovered its anterograde conduction partially, a divisional second degree A V block usually the Wenckebach type could be observed spontaneously (Figs. 6-8) or induced by atrial pacing (Fig. 7).

Definition of terms

A H time. The interval from the first deflection of the A wave to the first deflection of the BH electrogram.

H V time. Measured from the BH deflection to the earliest ventricular depolarization recorded on either the intracardiac electrogram or the peripheral lead.

A LB time. From the onset of the atrial electrogram to the recording site of the LB.

LB V time. Measured from the recording site of the LB to the earliest ventricular activation.

Results

On the 30 studied dogs the Luciani-Wenckebach (L W) periods were obtained in 24: 16 in the posterior division and 8 in the anterior division. This phenomenon could be repeated several times in different parts of the intraventricular conduction system during the same experiment.

The typical ECG recordings of a dog in the basal state are observed at the left of Fig. 2, where simultaneous recordings of the HBE and three standard leads are shown. At the right of the same figure (once the definitive section of the right bundle was performed) we see a widening of the QRS to 45 msec. and a notorious right and upward axis deviation in the frontal plane with the appearance of an rsR′ wave in V1. This is the characteristic pattern of the RBBB in the dog. The conduction time between the HB and the ventricular activation (H V) remained constant measuring 35 msec. in both normal and RBBB recordings.

Once the trifascicular complete A V block was performed (Fig. 5) and the posterior division recovered its conduction we observe in Fig. 6 conducted sinus beats with RBBB and left anterior hemiblock (LAH). At the same time we must mention that in the presence of a RBBB the anterior hemiblock makes the S wave deeper and diminishes the R wave establishing a very small r S relationship in Leads II and III. It also produces a Q wave in Lead I changing the rS complex into a qR complex. The P R interval of the first conducted P wave was prolonged; this delay is localized distal to the main stem of the LBB in its posterior division. This fact is demonstrated by the LB V interval prolongation. In the third beat we notice a progressive delay of the conduction in the intraventricular system produced by changes in the posterior division conductivity until a ventricular complex is dropped engendering a 3:2 conduction ratio. The said periods can also be obtained by

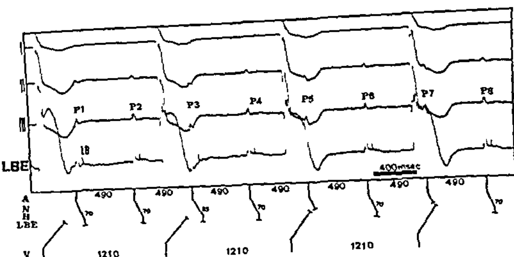


Fig 5 Complete trifascicular A V block Simultaneous recording of three standard lead and LBE. In the presence of a complete A V block the P wave followed by the LBE indicates that the anterograde conduction is blocked below the main stem of the LBB (see text)

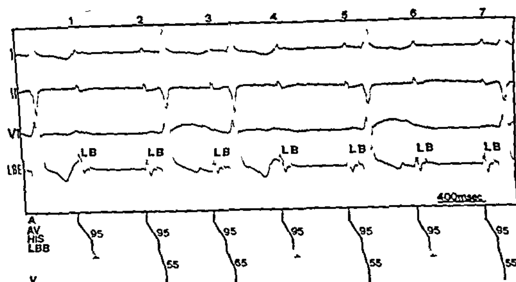


Fig 6 RBBB and LAH with Mobitz Type I block in the posterior division Simultaneous recordings of three electrocardiographic lead and LBBB electrogram Notice the progressive delay in conduction from 55 msec. to 65 msec. below the main stem of the LBB in the second and third beats until a ventricular complex is dropped in the fourth beat the A LB interval remaining constant at 95 msec. This illustrates a 3 2 Lucians Wenckebach cycle in the posterior division of the LBB In the fifth and sixth beats a 2 1 A V block is registered in the same division

increasing the heart rate with atrial pacing (Fig 7)

Fig 8 illustrates a RBBB with left posterior hemiblock (LPH) Note the marked changes that are caused by the LPH added to the one of RBBB deepening the S wave in D_I Note also the appearance of Q waves in D_{II} and D_{III} tall R waves in these leads and the shifting of the ÂQRS downward and to the right in the frontal plane From the third to the sixth beat we found a progressive prolongation of the LB V interval until a dropped beat occurred in the seventh with the development of a 5 4 L W cycle in the left anterior division The same phenomenon is also observed in Fig 9



Fig 4 Anteroposterior projection where the electrode catheters are observed A = passing arterially to just beyond the aortic valve V = reaching intravenously to the right intraventricular cavity

ized above the recording site caused by concealed retrograde conduction from the previous idioventricular beat The variations of the interval A LB depend on the magnitude of the coupling between the P wave and the preceding idioventricular beat determining that the stimulus reaches the transmembrane potential of the depolarized fibers during their refractory periods at different levels of repolarization

When the contused division recovered its anterograde conduction partially, a divisional second degree A V block, usually the Wenckebach type could be observed spontaneously (Figs 6 8) or induced by atrial pacing (Fig 7)

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Fig. 9 RBBB and LPH with Mobitz Type I block in the anterior division. Simultaneous recording of three electrocardiographic leads and LBB electrogram. The second P wave is conducted to the ventricles with an increased LB-V of 90 msec, becoming blocked in the third beat below the recording site of the electrogram causing a 2:1 block in the anterior division of the LBB. *Notice the beats become progressively slower in conduction below the main stem of the left branch during the fourth and fifth beats with the LB-V time increasing from 85 to 145 msec until a ventricular complex is dropped in the sixth beat with an A-LB time always remaining constant at 90 msec, showing a typical 3:2 L-W phenomenon in the anterior division of the LBB.*

trifascicular one has been proved[6] and Wenckebach periods in the right and left bundle branches have been indirectly demonstrated.[3] To prove the existence of the same phenomenon at the left bundle branch divisions (LBBD) we have used a technique for registering the LBE and transformed the intraventricular conduction system into a monofascicular one. This was performed by the production of a definitive blockade in both the RBB and one of the divisions of the LBB.

The particular trifascicular anatomical distribution of the His-Purkinje system is the determining factor of the multiple ECG variations that may be observed in Wenckebach periods of intraventricular conduction. These variables are conditioned by (1) the possibility of the existence of this form of impaired conduction in more than one fascicle, (2) their synchronism or asynchronism if the L-W periods are present in more than one of them, and (3) the existence of simultaneous transitory or definitive blockades in the other bundles or divisions (Figs. 10 and 12).

In the former illustration we observe a progressive intraventricular conduction delay in the third and fourth beats localized *in both divisions of the LBB* until a ventricular beat is dropped. The significant *morphological variation of the fourth beat is due to an increment of the left anterior hemiblock* characterized by deepening of the S wave and diminishing voltage of the R in D_{II}, establishing a very small r/S relationship in I and II. The increase of the *conduction time in the posterior division from 55 to 100 msec is responsible for the* prolongation of the LB-V interval. *This sequence shows a 3:2 L-W period in the posterior division of the LBB* in the presence of a RBBB with a transitory and progressive anterior hemiblock.

In Fig. 12 it is important to note in the fourth beat the paradoxical behavior of the posterior division which has been blocked. *This occurred* in spite of being preceded by a prolonged diastolic pause of 1020 msec. This blockage *is due to* the development of Phase 4 *depolarization* in the LPD of the LBB. On the contrary, the decrease in *H-V* and LB-V times indicates an improved conduction *in the LAD* of the LBB. These different forms of impaired *conduction* in both divisions show the evidence of two

Fig. 7 RBBB and LAH with Mobitz Type I block in the posterior division. Simultaneous recordings of three electrocardiographic leads and LBB electrogram during atrial pacing at 185/min. Notice that the second LB wave is conducted to the ventricle with an LB-V of 25 msec, becoming blocked in the third beat below the recording site of the electrogram giving rise to a 2:1 A-V block in the posterior division of the LBB. The corresponding auricular beats become progressively slower below the main stem of the left branch during the fourth and fifth stimuli with the LB-V time increasing from 25 to 45 msec until its complete interruption in the sixth beat, showing a typical 3:2 W phenomenon in the posterior division of the LBB.

Fig. 8 RBBB and LPH with Mobitz Type I block in the anterior division. Simultaneous recordings of three electrocardiographic leads and LBB electrogram. Notice the progressive delay in conduction from 90 to 150 msec below the main stem of the LBB from the third beat to its complete interruption in the seventh beat with a constant A-LB time of 60 msec, showing a 5:4 L-W phenomenon in the anterior division of the LBB.

Discussion

In the anatomical observations made in the mammalian and in the human heart[14] the existence of two terminal ramifications of the LBB were determined, namely the anterior and posterior divisions. These end either directly or by false tendons at their respective papillary muscles.

The fact that the canine intraventricular system is anatomically and functionally a

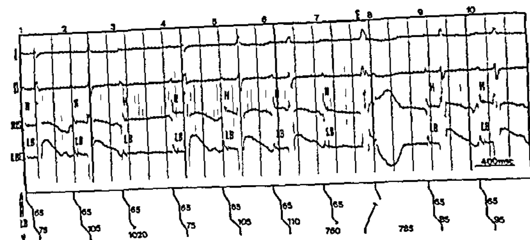


Fig. 12 Simultaneous recordings of two standard leads His and left bundle electrograms. In the fourth, fifth, sixth and seventh beat we observe a 4:3 L-W period in both divisions in the presence of an RBBB and a transitory LPH

diagram showing the conduction pattern

If there is a definitive blockade in two fascicles and a Wenckebach phenomenon in the other, it is evident that there would be a delay in the A-V conduction as happens in the two cases described above (Figs 6 and 8)

If the Wenckebach period occurred simultaneously in more than one fascicle [16] variable degrees of conduction delays in the branches or divisions would be present and the appearance of an A-V block would depend on how many fascicles were affected [17]

Considering that the LBB system is composed of a trunk and two principal subdivisions, the total interruption of its main stem (truncular block) or simultaneous blockage in both divisions (divisional block, see Fig 11) produced the same ECG pattern of LBBB. Therefore it may be suggested that the mechanism responsible for the L-W periods in the LBB [4] can be localized separately in the trunk or conjointly in both divisions

Various mechanisms causing failure of impulse propagation can occur simultaneously in the bundle branches. This has been demonstrated clinically by the coexisting L-W periods in one branch and Mobitz Type II block in the other [18] We confirmed in clinical [19] and experimental [20,21] studies that Phase 4 depolarization [22-25] has a close and intricate relationship in the genesis of the underlying electrophysiological mechanism that produces bradycardia dependent bundle branch [26,28] divisional [29] and A-V block [30] The combination of both particular forms of impaired conduction (Phase 4 depolarization and L-W periods) [31] was documented in Fig 12 where a Mobitz Type I A-V block in both divisions in the presence of a RBBB coexists with a transitory LPH related to Phase 4 depolarization. In support of this conclusion a similar isolated resultant disturbance in the posterior division of the LBB was facilitated by decreasing the cardiac rate (Fig 13). In this illustration we observe the shortening of the LB-V from 85 to 75 msec demonstrating that the improving conduction of the LAD is directly related to the previous prolonged pause induced by vagal stimulation (*arrow*). On the other hand paradoxically a bradycardia-dependent block is observed in the posterior division due to Phase 4 depolarization. Morphologically in this figure the third beat was identical to the first and fourth beats of Fig 12, their LB-V times and the polarity of the LB electrograms remained constant and their couplings were highly variable. Considering these findings ventricular escape beats were ruled out. In the bottom panel of Fig 13 the development of Phase 4 depolarization reduces the transmembrane potential below a critical level determining that the His escape (third beat) which

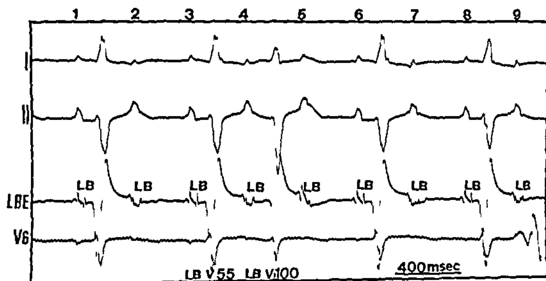


Fig. *10* RBB and incomplete LAH with second degree block in the posterior division of the LBB. Simultaneous recordings of three leads and LBE (see text).

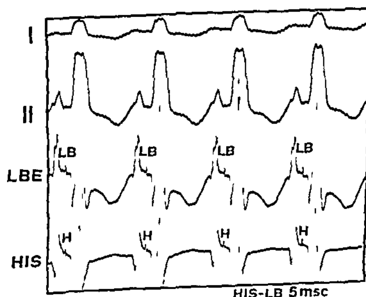


Fig. *11* Simultaneous recordings of two standard leads, His and left bundle electrograms. Divisional LBBB produced experimentally after sectioning the anterior and posterior divisions of the left bundle branch. The recording of the LBE in the presence of an LBBB indicates that the interrupted conduction is situated below the main stem in its divisions.

types of blocking mechanisms (1) the prolongation of the absolute and relative refractory periods which determine the block in Phase 3 and improve its conduction with a previous prolonged R R interval—this factor is responsible for the decrease of the LB V interval in the fourth beat and (2) the development of Phase 4 depolarization occurring in the affected fascicle giving rise to LPH in the same beat. A similar sequence is repeated in the first, second and third beat configuring a 3:2 Luciani-Wenckebach period. The ninth beat also preceded by a prolonged diastolic pause is conducted without developing an LPH. This is determined by the retrograde conduction from the ventricular escape (*E*) to the LBB re-establishing the levels of repolarization of the transmembrane action potential to limits that allow the conduction in both divisions, with a delay of only 10 msec. The retrograde depolarization from the escape beat (*E*) is evidenced by the anterograde block of the eighth P wave above the bundle of His. Below the experimental records is the corresponding ladder

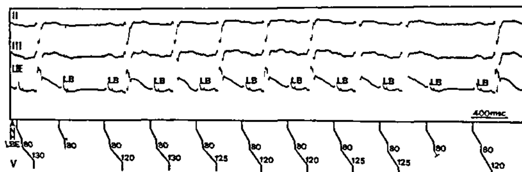


Fig 15 Same experiment as illustrated in Fig 14 Simultaneous recordings of two standard leads and LBE RBBB and LAH with first degree block in the posterior division of the LBB Transitional 8 7 L W period in the posterior division Observe the atypical form of A V conduction progressively impaired in the second and third beats a lessening of this disturbance in the fourth and fifth beats and again increasing in the sixth and seventh beats to become completely blocked in the eighth beat Notice an increment of delayed conduction (LB V interval) during this L W period of only 10 msec

anatomical vertical orientation a greater thickness of the right ventricle free wall a paraseptal implantation of the right papillary muscle absence of the moderator band and the greater length (0 4 cm) of the left bundle branch (trunk plus anterior division) compared to the right one [33] being reversed in the human subject where the right bundle is longer than the left [34] However the dog is the only mammal of those which we have studied that has a great likeness to the human trifascicular conduction system because a branching portion of the His bundle and a bidivisional ending of the LBB can be observed in both (Fig 1) This makes us suppose that the same conduction disturbances mentioned before can occur under different pathological situations in the human heart

Summary

Electrograms of the LBB were obtained in thirty dogs by left transventricular puncture or arterial retrograde catheterism The RBB and one of the LBBD were sectioned and the other was contused when this one recovered its conduction partially it was possible to obtain Wenckebach periods and transitional forms spontaneously or by atrial pacing

We suggested that the underlying mechanism of the L W cycle in the LBB can be localized separately in its main stem or simultaneously in both divisions

The coexistence of two different forms of impaired conduction (L W periods and Phase 4 depolarization) was demonstrated in the left bundle branch divisions

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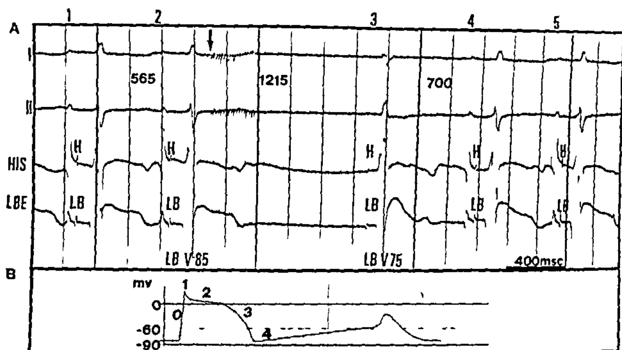


Fig. 13. Same experiment as illustrated in Fig. 12. *Top tracing:* Simultaneous recording of two standard lead His and left bundle electrogram. On the third beat a BH escape is conducted with RBBB and LAH. *Bottom tracing:* Schematic representation of transmembrane potential in the posterior division fibers of the LBB.

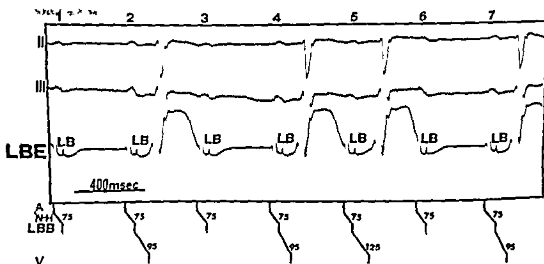


Fig. 14. Simultaneous recordings of two leads and LBE. LBBB with LAH and first degree block in the posterior division of the LBB. On the third, fourth, and fifth beats we observe a 3:2 L-W phenomenon in the posterior division with a progressive intraventricular conduction delay of 30 msec.

reaches the posterior division during the latter phase of diastolic depolarization will become blocked.

Despite the notorious frequence and the transient occurrence of the Wenckebach phenomena in our findings, we could not obtain Mobitz Type II block. But in several experiments (Fig. 14) L-W periods could be seen together with "transitional forms" (Fig. 15) that are characterized by increasingly progressive small delays in conduction (to 10 msec.). This decrease in the transmission pathway may not be apparent on the clinical ECG because its slow recording speed does not allow us to identify a conduction interval of less than 20 msec. Thus we suppose that some of the cases diagnosed clinically as Mobitz Type II block may be due to the L-W transitional forms described above.[32]

There are several differences between the canine heart and the human one, namely

Effect of aspirin upon experimental coronary and non coronary thrombosis and arrhythmia

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A number of studies have shown that acetylsalicylic acid (aspirin) may affect the participation of platelets in thrombus formation. Aspirin has displayed a consistent impairment of the platelet aggregation response to connective tissue and also inhibition of the secondary phase of platelet aggregation in the presence of ADP or epinephrine.[1-5] In view of the fact that platelet aggregation constitutes the most important initial step in the formation of thrombus,[6] speculation has arisen on the potential effects of salicylates upon arterial thrombogenesis in vivo.[7] An evaluation of such effects could be obtained only by using an experimental model favoring the formation of a platelet thrombus similar to that occurring spontaneously in the arterial system. Such a thrombus can be induced in the coronary or peripheral artery of the intact animal by means of a catheter electrode as described below. The effects of acetylsalicylic acid (ASA) upon such a thrombus is the objective of the present study.

Materials and methods

A total of 109 apparently healthy mongrel dogs fasting for 18 hours and weighing from 19 to 25 kilograms was used. The animals were anesthetized with sodium pentobarbital (25 mg. per kilogram of body weight intravenously) and placed on a respiratory pump to maintain adequate ventilation. The left carotid artery, left jugular vein, and the left femoral vein were exposed through small skin incisions. Seventy-nine of the animals were given aspirin as described below, whereas 30 animals were used as controls. The animals receiving ASA were divided into two general groups: a group where coronary thrombus formation was attempted following aspirin administration given stat or daily for seven days prior to the experiment, and another group with thrombus formation attempted in the femoral artery after receiving aspirin likewise administered immediately or daily for seven days prior to the experiment. The formation of a platelet thrombus in one of the branches of the left coronary

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Table I Coronary artery thrombosis

Groups	Aspirin mg/kg		Early thrombus	Late thrombus	Thrombus formed		Thrombus weight (mg)		Arrhythmias		Ventricular fibrillation	
	Orally	i v	No of animals	No of animals	No of animals	P*	Mean and S.E	P	No of animals	P*	No of animals	P*
Controls	—	—	8	—	7		31 ± 3 3		7		5	
	—	—	—	8	8		38 ± 8 7		8		7	
					6	NS	48 ± 1 .3	NS	5	NS	3	NS
Controls-placebo	—	—	6	—	14		23 ± 6 6†		5		1	
1A	30	—	17	—		NS		NS		<0 01		<0 01
	60	—	4	—	4		4 ± 4 9		1		—	
1B	30	—	—	5	5		71 4 ± 18.5		3		1	
						NS		NS		<0 01		<0 01
	60	—	—	[illegible]	4		4[illegible] ± 23 1				—	
A	—	30	3	—			34 ± 3 8		1		—	
						NS		NS		<0 01		<0 01
	—	60	3	—	3		3[illegible] ± 1[illegible].5		1		—	
B	—	30	—	5	4		6[illegible].2 ± 19 6		[illegible]			
						NS		NS		<0 01		<0 01
	—	60	—	8	6		69 2 ± 4 7		4		[illegible]	
3	30	—	—	10	7	NS	[illegible]0 3 ± 8 1	NS	3	<0 01	1	<0 01

Tl d sag f h g p w omb ed fo t tl t cal ly s a d w re mpa d to mb ned co t ol
†I 12 d g
‡Th s dosag is pp ox m t ince 600 mg a pun we e g n d ily fo se d ys to all d g weigl g 19 to 22 k fog am

Table II Femoral artery thrombus

Groups	Early thrombus	Aspirin orally (mg/kg)	Thrombus formed	Thrombus weight
Control	8	0	7	26 3 ± 5 3
A pirin tat	8	60	8	34 3 ± 9 2
A pirin daily	11	30	11	37 5 ± 8 3

*This dosag pr x m t nce 600 mg asp ri were gi daily f se d ys t all dog w gh g 20 t 25 k l gram

subsequently was given by continuous infusion which was started a half hour prior to the induction of thrombosis and was continued for the duration of the current application Autopsy was performed either at the end of 90 minutes of current application (the early thrombus group) or three hours following the 90 minute period of current application (the late thrombus group) In order to evaluate the effects of dosage and route of administration of aspirin upon the incidence and size of thrombus the two general groups of coronary and femoral artery thrombosis were subdivided into different categories Table I shows the coronary thrombus group Two categories of controls were used one of which received placebo tablets instead of aspirin The early thrombus groups (1A and 2A) and late thrombus groups (1B and 2B) received aspirin stat by mouth or intravenously in the same manner and in specified dosages of 30 or 60 mg per kilogram of body weight A separate category of the coronary thrombosis Group 3 consisted of animals which were given aspirin by mouth approximately 30 mg per kilogram of body weight daily for seven days prior to the experiment and comprised only late thrombus dogs The femoral artery thrombus group (Table II) comprised a control and two groups with early thrombus only one receiving aspirin stat by mouth 60 mg per kilogram of body weight and the other daily 30 mg



Fig 1 Photomicrograph of anterior descending coronary artery with a platelet thrombus produced by an electrode catheter (Hematoxylin and eosin Original magnification ×75)

artery was induced by means of a catheter electrode placed by way of the left carotid artery in the proximal 1 to 2 cm segment of the left anterior or circumflex coronary artery [8] A 300 to 500 microampere current applied on the intima induces a platelet thrombus within 15 to 90 minutes without causing gross intimal and subintimal injury as when the current is greater than 600 microamperes Morphologically the formed thrombus (Fig 1) is similar to that described in human arteries [9,10] Thrombus formation in this model is usually indicated by the appearance of an acute injury potential and multiple premature ventricular contractions in the continuously monitored ECG Occasionally, despite the formation of a thrombus as proved at autopsy the ECG findings are not definitely diagnostic, particularly in regard to the appearance of injury potential On the other hand, the appearance of the ST elevation can occasionally be due to mechanical obstruction of the coronary vessel by the inserted catheter However in our experience, the injury potential in this case appears within the first one or two minutes following the placement of the catheter into the coronary artery and prior to the induction of current The earliest appearance of ST elevation due to the presence of an obstructing thrombus as proved by coronary angiogram, autopsy, and ECG changes is approximately 15 minutes following the placement of the catheter and the induction of electric current We therefore excluded from the study a total of five animals in which ST elevation appeared in the first few minutes, following the placement of the catheter The ECG was observed throughout the entire period of the experiment recording the frequency of arrhythmias The reproducibility of this method for thrombus formation is in our hands approximately 90 per cent An estimate of the platelet adequacy was made in each dog prior to experiment since in our experience, when the platelet count is below 40 000 per cubic millimeter, a thrombus fails as a rule to develop by this method Formation of a thrombus in the femoral artery was attempted in the intact dog by the same method modified as follows

A 130 cm single strand insulated wire gauge 20 was passed through a No 7F radiopaque catheter about 125 cm long filled with normal saline solution and locked with a stopcock Subsequently using the left carotid artery, the catheter was placed under fluoroscopic control and by way of the descending aorta into the femoral artery approximately 9 to 10 cm below the bifurcation of the aorta The intensity of the current used in this case was 500 microamperes for 90 minutes The dose of aspirin given either by mouth or intravenously was 30 or 60 mg per kilogram of body weight When given by mouth aspirin was crushed suspended in normal saline solution and by means of a Levin tube was injected into the stomach This was followed by a waiting period of two hours prior to induction of thrombosis For intravenous administration, aspirin* was freshly dissolved in Tyrode s solution adjusted to pH 7 4 and

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Table I Coronary artery thrombosis

Groups	Aspirin mg /kg		Early thrombus	Late thrombus	Thrombus formed		Thrombus weight (mg)		Arrhythmias		Ventricular fibrillation	
	Orally	i v	No of animals	No of animals	No of animals	P	Mean and S E	P*	No of animals	P*	No of animals	P*
Controls	—	—	8	—	7		31 ± 3 3		4		5	
	—	—	—	8	8		38 ± 8 7		8			
Controls-placebo	—	—	6	—	6	NS	48 ± 17 3	NS	5	NS	3	NS
1A	30	—	17	—	14		23 ± 6 6†		5		1	
						NS		NS		<0 01		<0 01
	60	—	4	—	4		24 ± 4 9		1		—	
1B	30	—	—	5	5		71 4 ± 18 5		3		1	
						NS		NS		<0 01		<0 01
	60	—	—	5	4		45.2 ± 23 1				—	
2A	—	30	3	—			34 ± 3 8		1		—	
						NS		NS		<0 01		<0 01
	—	60	3	—	3		3 ± 1 8		1		—	
2B	—	30	—	5	4		69 [illegible] ± 19 6				2	
						NS		NS		<0 01		<0 01
	—	60	—	8	6		69 [illegible] ± 4 7		4			
3	30	—	—	10	7	NS	90.3 ± 8 1	NS	3	<0 01	1	<0 01

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Table II Femoral artery thrombus

Groups	Early thrombus	Aspirin orally (mg /kg)	Thrombus formed	Thrombus weight
Control	8	0	7	26 3 ± 5 3
A pirin tat	8	60	8	34 3 ± 9 2
Aspirin d ly	11	30	11	3 5 ± 8 3

*Th d sa e pp t l ce 600 mg a r w g n d ly f r se d y to all dog w gh g 20 t 25 k l gram

subsequently was given by continuous infusion which was started a half hour prior to the induction of thrombosis and was continued for the duration of the current application Autopsy was performed either at the end of 90 minutes of current application (the early thrombus group) or three hours following the 90 minute period of current application (the late thrombus group) In order to evaluate the effects of dosage and route of administration of aspirin upon the incidence and size of thrombus the two general groups of coronary and femoral artery thrombosis were subdivided into different categories Table I shows the coronary thrombus group Two categories of controls were used one of which received placebo tablets instead of aspirin The early thrombus groups (1A and 2A) and late thrombus groups (1B and 2B) received aspirin stat by mouth or intravenously in the same manner and in specified dosages of 30 or 60 mg per kilogram of body weight A separate category of the coronary thrombosis Group 3 consisted of animals which were given aspirin by mouth approximately 30 mg per kilogram of body weight daily for seven days prior to the experiment and comprised only late thrombus dogs The femoral artery thrombus group (Table II) comprised a control and two groups with early thrombus only one receiving aspirin stat by mouth 60 mg per kilogram of body weight and the other daily 30 mg



Fig 1 Photomicrograph of anterior descending coronary artery with a platelet thrombus produced by an electrode catheter (Hematoxylin and eosin Original magnification ×75)

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A 130 cm single strand insulated wire, gauge 20 was passed through a No 7F radiopaque catheter about 125 cm long filled with normal saline solution and locked with a stopcock Subsequently, using the left carotid artery the catheter was placed under fluoroscopic control and by way of the descending aorta into the femoral artery approximately 9 to 10 cm below the bifurcation of the aorta The intensity of the current used in this case was 500 microamperes for 90 minutes The dose of aspirin given either by mouth or intravenously was 30 or 60 mg per kilogram of body weight When given by mouth, aspirin was crushed suspended in normal saline solution, and by means of a Levin tube was injected into the stomach This was followed by a waiting period of two hours prior to induction of thrombosis For intravenous administration, aspirin* was freshly dissolved in Tyrode s solution adjusted to pH 7 4 and

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Table I Coronary artery thrombosis

Groups	Aspirin mg/kg		Early thrombus	Late thrombus	Thrombus formed		Thrombus weight (mg)		Arrhythmias		Ventricular fibrillation	
	Orally	i.v.	No of animals	No of animals	No of animals	P*	Mean and S.E.	P	No of animals	P*	No of animals	P*
Controls	—	—	8	—	7		31 ± 3.3		7		5	
	—	—	—	8	8	NS	38 ± 8.7	NS	8	NS	3	NS
Controls-placebo	—	—	6	—	6		48 ± 17.3		5		1	
1A	30	—	17	—	14	NS	23.– ± 6.6†	NS	5	<0.01		<0.01
	60	—	4	—	4		4 ± 4.9		1		—	
1B	30	—	—	5	5	NS	71.4 ± 18.5	NS	3	<0.01	1	<0.01
	60	—	—		4		4 ± 23.1				—	
2A	—	30	3	—		NS	34 ± 3.8	NS	1	<0.01	—	<0.01
	—	60	3	—	3		35 ± 1.8		1		—	
2B	—	30	—	5	4	NS	69.2 ± 19.6	NS	2	<0.01	2	<0.01
	—	60	—	8	6		69 ± 24		4			
3	30	—	—	10	7	NS	203 ± 8.1	NS	3	<0.01	1	<0.01

*The ... were combined for statistical analysis ... were compared to combined control
†... 12 dogs.
‡The dosage ... 600 mg aspirin were given daily ... all dogs weighing 19 to 22 kilogram

Table II Femoral artery thrombus

Groups	Early thrombus	Aspirin orally (mg/kg)	Thrombus formed	Thrombus weight
Control	8	0	7	26.3 ± 5.3
Aspirin stat	8	60	8	34.3 ± 9.2
Aspirin daily	11	30	11	37.5 ± 8.3

The dosage ... 600 mg aspirin were given daily ... all dogs weighing 20 to 25 kilogram

subsequently was given by continuous infusion which was started a half hour prior to the induction of thrombosis and was continued for the duration of the current application. Autopsy was performed either at the end of 90 minutes of current application (the early thrombus group) or three hours following the 90 minute period of current application (the late thrombus group). In order to evaluate the effects of dosage and route of administration of aspirin upon the incidence and size of thrombus the two general groups of coronary and femoral artery thrombosis were subdivided into different categories. Table I shows the coronary thrombus group. Two categories of controls were used, one of which received placebo tablets instead of aspirin. The early thrombus groups (1A and 2A) and late thrombus groups (1B and 2B) received aspirin stat by mouth or intravenously in the same manner and in specified dosages of 30 or 60 mg per kilogram of body weight. A separate category of the coronary thrombosis, Group 3, consisted of animals which were given aspirin by mouth approximately 30 mg per kilogram of body weight daily for seven days prior to the experiment and comprised only late thrombus dogs. The femoral artery thrombus group (Table II) comprised a control and two groups with early thrombus only, one receiving aspirin stat by mouth 60 mg per kilogram of body weight and the other daily 30 mg

Table III Salicylate blood levels before induction of thrombosis

Route administration	Aspirin (mg/kg)	No of animals	Blood level (mg/100 ml) average and range
By mouth stat	30	6	7 1(6 1-3 5)
	60	6	11 8(9-15 5)
Intravenous infusion	30	7	10 9(10 4-12 5)
	60	6	14 9(11-23)
Daily for seven days	30	10	8 7(5 9-16 2)

per kilogram of body weight for seven days prior to the experiment Determination of salicylate levels in blood was carried out in several dogs of each group using the method of Trinder[11] In the coronary artery thrombus group the incidence of arrhythmias and mortality during thrombus formation was recorded Following autopsy the incidence of thrombus formation, its location and weight were evaluated in all dogs The results were statistically evaluated applying the non paired observation formula for thrombus weight For the rest of the results the χ formula with one degree of freedom was applied

Results

Coronary artery thrombus The effects of aspirin upon coronary thrombosis are shown in Table I Regarding incidence a thrombus was found in the coronary artery in the overwhelming majority of the early as well as the late thrombus groups The average weight of the thrombi in the various categories of early thrombus was found to be smaller or very close to that of the control group, however, the differences were not statistically significant Increasing the dosage from 30 to 60 mg per kilogram of body weight did not significantly affect the average weight of the thrombi In regard to the late thrombus the recovered thrombi at autopsy were larger than the corresponding control group particularly when the aspirin was given intravenously However the animals of Group 3 receiving aspirin daily for seven days had an average thrombus weight smaller than the control and in three of these animals no thrombus was formed Due to the scatter in thrombus size the differences from the control group were not significant On the other hand all dogs receiving aspirin by any route of administration showed a significant decrease in incidence of arrhythmias when compared to corresponding controls of early and late thrombus ($p < 0.01$) This observation was matched with considerable decreases in the incidence of mortality ($p < 0.01$) due in this preparation to ventricular fibrillation[12]

Femoral artery thrombus Table II shows the results in the group with thrombus in the femoral artery It is evident that aspirin given either stat or daily for seven days did not avert the formation of thrombus in the femoral artery Moreover the average weight in this case was higher than the weight in the control group although the difference was not statistically significant

Table III shows the average and range of aspirin blood levels just prior to the induction of thrombosis The level was dependent on the route of administration and dosage being higher when aspirin was given intravenously In Group 3 with daily administration of aspirin by mouth, the average level was somewhat higher than the groups receiving the same dosage of aspirin stat by mouth Several blood samples taken during as well as at the end of the experiment showed that the ASA level was declining two to four hours following the last administration either by mouth or intravenously

Discussion

The results of this study suggest that under the conditions of the experimental procedure used to induce peripheral and coronary artery thrombi as well as the mode of treatment with aspirin the thrombotic process in the arteries was not pre

vented The incidence of thrombus formation in all groups was comparable to the control group Although in several categories of coronary thrombus groups the formed thrombi tended to be somewhat smaller than in the corresponding controls due to wide scatter in size of thrombus the differences were not statistically significant In the femoral artery group there was no effect of aspirin upon thrombus formation as can be judged by the size of the thrombi which in the two treated groups displayed a larger average weight than in the control group The dosage of aspirin used in this study was sufficient for a 19 to 25 kilogram animal to produce blood levels which affect platelet function for several days[4] These findings are in contrast to the results reported by Danese Voleti and Weiss[13] who found a prophylactic effect of aspirin upon thrombus formation in the femoral artery of dogs using as the criterion the degree of obstruction rather than the incidence of thrombosis This difference might be due to their technique of producing thrombosis involving direct surgical approach to the artery with injury to the wall induced chemically or surgically The nature of the stimulus for the production of a thrombus may determine the type of the thrombus to be formed It is recognized that the occurrence of thrombi in disease states can be determined by other variables which may not necessarily relate to the mode of thrombus production in the present study However the possibility of a non predominantly platelet thrombus in the report of Danese Voleti and Weiss[13] must be considered since a prophylactic effect of aspirin upon venous thrombosis and thromboembolism in which the thrombus is structurally different from an arterial thrombus has been reported[14,15] Earlier Evans and associates[3] reported a decrease in platelet deposits in extracorporeal shunts in rabbits following administration of very high aspirin dosage[3]

The distinct difference from controls in incidence of arrhythmias and ventricular fibrillation observed in the coronary thrombus group treated with aspirin was unexpected Arrhythmias and ventricular fibrillation in control animals with an early or late thrombus have been observed to occur in about 50 per cent and 90 per cent respectively[12] The reasons for these differences are not clear at this time If this observation were made in the early thrombus group it could be at least partly associated with the size of the thrombus since in about the half of the animals in the early thrombus group the thrombus was smaller causing probably lesser degree of obstruction and interfering less critically with regional coronary blood flow However the same explanation cannot be applied to the late thrombus group There the incidence of arrhythmias and ventricular fibrillation was lower even though the size of the thrombi was significantly higher than control except for Group 3 where the thrombus was smaller and three out of ten animals had no thrombus In a recent study we found that following the formation of a thrombus in the coronary artery platelet aggregates or thrombi are formed in the microcirculation which occurrence we consider to constitute a part of a recent thrombotic process in a major coronary vessel[16] Subsequently we observed that aspirin and dipyridamole in a small daily dose reduce significantly the incidence of platelet aggregates in the microcirculation although these drugs failed to affect the incidence of thrombus formation in the larger coronary vessels of the same animals (unpublished data) Further investigation is necessary to establish any relevance of these findings particularly of platelet and other cell function to the incidence of arrhythmias in animals receiving aspirin—which is known for its broad effects upon cell metabolism[17]

Numerous animals receiving aspirin displayed a tendency for larger thrombi particularly in the late thrombus group The reason for this occurrence with aspirin is not clear at this time In view of the profound metabolic effect of salicylates[17] the question is raised whether among others their property to acetylate plasma proteins and particularly albumin[18] might be relevant since plasma proteins were found to interfere with platelet surface reactivity[19,20]

Summary

The effect of aspirin upon platelet function led to speculation on the potential effects of salicylates upon arterial thrombogenesis in which platelets play a primary role Aspirin was given by mouth or intra

venously before attempting induction of coronary or femoral artery thrombosis in dogs by means of a catheter electrode. The incidence of thrombus formation in all animals receiving aspirin was comparable to that of the control groups. Although in several animals of coronary thrombus group receiving aspirin the thrombus was smaller than in the controls this was not statistically significant. An unexpected finding was the distinct decrease in incidence of arrhythmias and ventricular fibrillation in the coronary thrombus group treated with aspirin. The reason for the differences is not clear at this time.

The authors wish to thank Miss Elaine Podell and Mrs Amparo Lcobina for technical assistance and Mrs. Marilynn Littman for secretarial service rendered.

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Case reports

Right-sided cervical aortic arch

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The first case of a cervical aortic arch was reported in 1947 by Beaven and Fitti[1] who discovered the rare anomaly after their disastrous ligation of what appeared to be an aneurysm of the right innominate artery. Ten more cases were subsequently reported, in all but two of which the cervical arch was right sided.

We describe the twelfth case of cervical aortic arch. This is the second reported case in an adult patient and the first where the ipsilateral carotid vessel fails to originate from the apex of the cervical aorta. In this patient, the right external carotid vessel arises separately from the ascending portion of the aorta just above the origin of the left carotid artery—a finding which may be significant to the debate over whether this anomaly represents a persistence of the third or the fourth branchial arches.

Case report

The patient was a 30-year old woman in whom a cardiac murmur and blood pressure abnormality were first noted during her third and most recent pregnancy. She underwent further cardiac evaluation after delivery; her medical history was remarkable only for prior recurrent chronic bouts of hoarseness and dysphagia.

Physical examination revealed a blood pressure of 130/80 mm. Hg in the right arm, 105/80 mm. Hg in the left arm, and a systolic pressure of 90 mm. Hg in the legs. Pulses in the extremities were weak, and femoral pulses were abnormally delayed in comparison with the carotids, which were equal and hyperkinetic.

The cardiac point of maximum impulse was hyperdynamic and in the fourth intercostal space in the midclavicular line. The jugular venous pressure was not elevated and no parasternal heave was evident. A large (? by 4 cm.) pulsatile mass occupied the right supraclavicular fossa and extended up into the right side of the neck. Its impulse coincided with systole. Over the mass a thrill was palpable and a Grade IV/VI harsh, mid-to-late systolic ejection murmur was heard radiating over the precordium as well as into the posterior lung field. The abdominal aorta was not palpable and there were no bruits over the abdomen or chest cage.

A presumptive diagnosis of coarctation of the aorta was made. Laboratory data were noncontributory. Roentgenogram of the chest revealed an abnormal superior mediastinum with the aortic knob barely visible and a dense area adjacent to the cervical vertebrae on the right above the clavicle. No rib notching was seen. The electrocardiogram (ECG) was normal.

On barium swallow, the anomalous aortic arch was delineated with anterior and right lateral displacement of the esophagus seen at the level of T3

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Fig. 1. Roentgenograms of chest with barium in esophagus reveal normal heart size, high right deviation of esophagus, and apparent left aortic knob.

Displacement was caused by the pulsatile aorta which was partially visible in the apex of the right chest and apparently descended in a normal left position (Fig. 1). Cineangiocardiographic and Elema angiocardiographic studies showed that the patient had a right aortic arch. The ascending aorta extended up into the right side of the supraclavicular area, made a turn, passed retroesophageally, and then descended on the left (Figs. 2 to 4). There was an associated aortic diverticulum at the level of the left subclavian artery but no evidence of coarctation. Although blood pressure gradually declined as the aorta was traversed, it did not abruptly change at any level.

Discussion

In all but one of the eleven previously reported cases of cervical aortic arch, patients were aged ten years or less. Respiratory symptoms suggestive of a vascular ring are common, as are pulse and blood pressure discrepancies.[1-7] Two other patients besides ours also had dysphagia.[1,2] In virtually every case a large pulsating cervical mass was seen and in at least three instances led to a clinical impression of aneurysm of the common carotid artery.[1,8,9] When cervical aortic arch is suspected, however, diminution of the femoral pulses by compression of the pulsating mass against the adjacent vertebrae provides a pathognomonic clinical maneuver.[9] Diagnosis can be confirmed by aortography.

The cervical aortic arch was *right sided* in nine cases, including ours. The first branch off the ascending aorta was a separate left common carotid artery, and the right carotid artery, except in our patient, arose from the apex of the cervical portion of the arch. Gravier and co-workers[3] found that in their patient the right carotid artery originated with the right subclavian artery from a right brachiocephalic trunk that arose from the cervical apex, while Beaven and Fatti,[1] as D'Cruz and his associates[4] and Shepherd and co-workers[9] reported that the right internal and external carotid arteries originated separately from the apex of the arch. The right carotid artery was atretic in Massumi's[2] patient. In our patient the right external carotid originated

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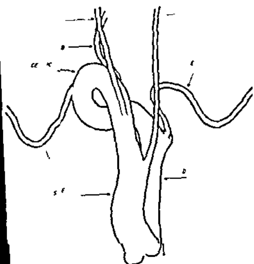


Fig 2 Ascending aortography reveals right cervical aorta First branch is left common carotid artery The right external carotid (*A*) arises next off of the ascending aorta The separate right internal carotid (*B*) can be seen arising at the apex of the cervical arch as the third brachiocephalic vessel The right subclavian artery arises as fourth branch from distal cervical aorta and left subclavian arises last from diverticulum of Kommerell Transverse portion of descending cervical aorta passes retroesophageally

separately from the ascending aorta just distal to the origin of the left common carotid artery

Except for the case of Gravier and co workers[8] the right subclavian artery originated distal to the cervical apex in all patients Although Gravier did not discuss the origin of the left subclavian artery all other authors noted that it arose together with the ductus arteriosus (or ligamentum) as a conical diverticulum from the descending aorta just after it emerges from behind the esophagus on the left

In one patient with a *left sided* cervical aortic arch the first branch off the ascending aorta was a right common carotid artery The right subclavian artery arose as the last branch off the descending aorta and the left external and internal carotids arose separately from the apex[10] In the other two patients the right carotid artery had its origin with the subclavian as an innominate artery[4,7] Both patients had the left common carotid artery arising from the apex of the cervical arch

Several theories have been advanced to explain the pathogenesis of the cervical aortic arch Beaven and Fatti[1] postulated that the reason for separate origin of the right external and internal carotid arteries was that the third right arch and ductus caroticus persisted while the fourth right arch did not Harley[11] on the other hand suggested that a persistent fourth right arch and ductus caroticus would also allow the right external and internal carotid to arise separately He argued that with either arrangement the right subclavian artery would form the third branch off the right sided aortic arch and the left subclavian artery which arose from the eighth segment of the left paired dorsal aorta would form the fourth branch off of the aorta Thus neither the third nor fourth embryologic aortic arch could be positively designated as the beginning of the formation

According to D Cruz and associates[5] the right third and fourth arterial arches may have become confluent at a phase when the primitive arches were cervically located perhaps due to anomalous growth of the pharyngeal pouch tissue in that area D Cruz theorized that if the left fourth arch anterior to the subclavian atrophies the left subclavian will be the fourth and last branch off the descending aorta or if the dorsal aorta above the subclavian atrophies the left subclavian will arise from the innominate branch

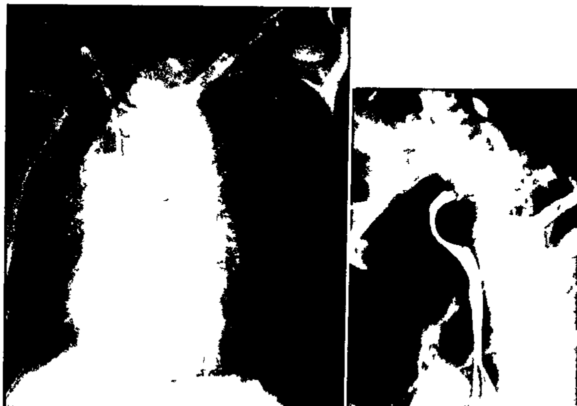


Fig. 3. Left anterior oblique views of passage of catheter through aorta. Barium swallow delineates retroesophageal course of aorta.



Fig. 4. Right anterior oblique views of passage of catheter through aorta. Barium swallow further demonstrates position of cervical aorta in relation to supraclavicular fossa.

Understanding the embryology of cervical aortic arch may be simplified by using the concept of Edwards[1] primitive pattern and applying the criteria set forth by Blake and Manion[11] for localizing the possible points of involution (Fig 5) The anomaly in our patient can be explained as a right aortic arch with involution at position 5 between the carotid and subclavian arteries on the left (see Fig 5) Normally of course the arch is left sided with involution at position 1 distal to both the carotid and subclavian arteries on the right

In addition to the involution at position 5 the cervical portion of the right arch which appears as an elongated accessory or redundant portion of the arch implies a further embryologic abnormality The very redundant nature of the cervical arch plus the distinctly separate origins of the right internal and external carotids support the thesis that this represents a persistence of the third right arch rather than a failure of descent of the fourth right arch along with persistence of the ductus caroticus on the right Absolute proof of either concept will be dependent upon the eventual identification of some nonvascular structure that passes or lies between the embryologic third and fourth arches and is not involved in the resorptive processes

Summary

Cervical aortic arch is a rare congenital anomaly that should be suspected in a patient with a large pulsatile supraclavicular mass Pulse and blood pressure abnormalities are frequently present as are symptoms suggestive of an intrathoracic vascular ring Diminution of femoral pulses by compression of the supraclavicular mass against cervical vertebrae is a valuable clinical maneuver for diagnosis of this condition which can be confirmed on aortography

A 30 year-old woman with a right sided aortic arch is the twelfth reported case of this anomaly This is the first case where the ipsilateral external carotid vessel arises separately from the intrathoracic portion of the aorta instead of from the apex of the cervical arch The actual redundant nature of the cervical arch plus the separate origins of the right internal and external carotid support but do not prove the thesis that the cervical arch represents a persistence of the embryonic third arch

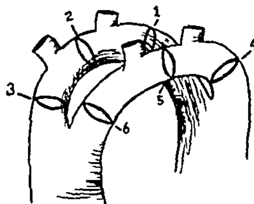


Fig 5 Drawing showing Blake and Manion [11] criteria for localizing possible points of involution (numbered 1 through 6) on aortic arches Ascending aorta passes dorsally as twin fourth arches to form descending aorta Each arch develops carotid and more dorsally subclavian branches (From Blake H A and Manion W C Circulation 26 251 1962 Reproduced by permission of The American Heart Association Inc)

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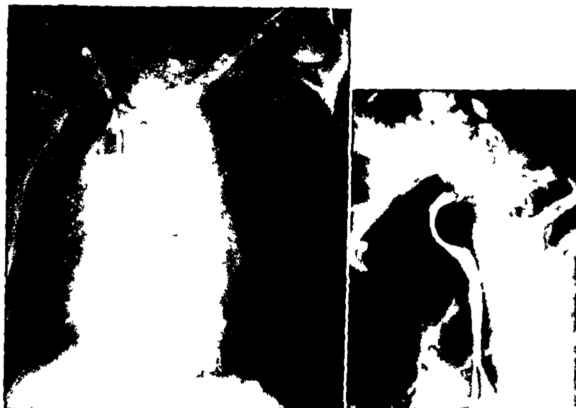


Fig. 3 Left anterior oblique views of passage of catheter through aorta Barium swallow delineates retroesophageal course of aorta



Fig. 4 Right anterior oblique views of passage of catheter through aorta Barium swallow further demonstrates position of cervical aorta in relation to supraclavicular fossa

Thromboembolism with the intracaval umbrella

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Passage of an umbrella into the inferior vena cava has recently become possible as an alternative to caval ligation in patients with recurrent pulmonary embolism The patient reported on below developed serious thromboembolic complications related to the prosthesis

Case report

A 28 year-old man entered another hospital because of sudden left sided pleuritic chest pa n dyspnea and hemopty i After the diagnos of acute pulmonary embolism was establi hed an umbrella was inserted into hi inferior vena cava through the r ght internal jugular vein Venography of both lower extremities performed just before the umb ella procedure was normal The patient s hospital course was smooth and he was discharged with a pre cription for Coumadin The patient stopped taking Coumadin shortly thereafter and did not return to the clinic

Six weeks after the umbrella insertion he began to notice pro ress ve pain and swell ng of his calves and th ghs One week later he was admitted to the Coney Island Hospital with right s ded pleur tic chest pa n and hemoptysis Physical examination revealed a well-developed and well nouri hed Caucasian man n moderate di tress because of chest and le pain The blood pres ure was 140/80 pulse rate 125 per minute and regular respiration rate 3? per minute and temperature 101 F Examination of the chest revealed mild plinting of the right side The lungs were clear and the neck veins flat Cardiac and abdominal examination was normal.

Both lower extremities were grossly swollen and warm with marked pitting of the calves and thighs Severe tenderness could be elicited particularly along the gastrocnemius areas and the medial portion of the th ghs. All peripheral pulses were palpated except the posterior tibial pulses which were obscured by the edema.

Laboratory data were as follows hemoglobin 11 5 Gm per 100 ml white blood count, 6 100 per cubic millimeter platelet count 3?4 000 per cubic millimeter urinalysis normal blood urea nitrogen 18 3 mg per 100 ml 2 hour postprandial blood sugar 106 per milligram per 100 ml prothrombin time normal serology negative lupus erythematosu preparations negative × 2 serum electrophoresis normal cryo lobulin determination negative electrocardiogram normal chest x ray showed focal atelectasis at the right base

Hospital course Since bilateral iliofemoral thrombophlebitis and acute pulmonary embolism were strongly su pected clinically heparinization was begun immediately A lung scan with macroaggregated human ¹³¹I albumin revealed defective perfusion at both bases and in the left superior field Pulmonary angiography revealed cut offs of blood flow in the segmental vessel of the right lower and

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the only morbidity being migration of the umbrella into a pulmonary artery in four cases On the other hand Neimat and Nabseth[5] reported a high incidence of clot on the cephalad surface of umbrellas placed in the inferior venae cavae of dogs

Since turbulent flow is unavoidable just distal to a venous obstruction it is not surprising that a thrombus often develops just inferior to the point of closure after inferior vena cava ligation In this situation a nonendothelialized foreign body may act as a nidus for propagation of these thrombi in a manner analogous to prosthetic heart valves This is the probable mechanism for the massive bilateral ilio femoral and caval thrombosis in our patient clinical thrombophlebitis after caval ligation is unusual[6,7] Once the lower surface of the umbrella is clotted no venous flow occurs through the fenestrations and a cul de sac with stagnation of blood and consequent clotting is likely to develop proximal to the prosthesis unless it is placed just below the entrance of an adequate sized vein into the cava Therefore one attempts to wedge the umbrella just distal to the renal veins but the position of the latter is only approximated from the intravenous pyelogram The present case demonstrates the inaccuracy of this method of estimation since the umbrella was found 2½ inches below the renal veins If thrombus propagation occurs on the proximal surface the danger of pulmonary embolism may be as great as or greater than it was before passage of the umbrella

In view of our experience with this patient we believe that patients with umbrella prostheses should be watched closely for the development of venous thrombosis and should be kept adequately anticoagulated In addition to clinical observations venography before and after insertion is advisable in order to ascertain the frequency of this complication Until more data are available we believe that caval umbrellas should be reserved for those patients with recurrent pulmonary embolism in whom inferior vena cava ligation poses a particularly high surgical risk of death

Summary

The recent introduction of an intracaval umbrella for prevention of pulmonary emboli has been followed by favorable comments concerning its efficacy We report a patient who developed serious thromboembolism following umbrella insertion associated with thrombus on both the inferior and superior surfaces of the prosthesis There is reason to suspect that potential clotting may be a significant drawback to this technique

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Fig. 1. Demonstration of occlusion of the right common femoral venous system with a clot visible in its more proximal aspect.



Fig. 2. Thrombus filling defects in the left external common iliac system with reflux into the perivesicular and median femoral circumflex veins. A meniscus is seen 5 mm proximal to the umbrella tip.

left upper lobes. Positive venographic findings included complete occlusion of the right common femoral system (Fig. 1). A left-sided common femoral vein puncture demonstrated a thrombus within the left external iliac common iliac system with meniscus formation 5 mm below the tip of the umbrella at the upper level of the third lumbar vertebra suggesting clot formation on its convex surface (Fig. 2). Reflux into the median femoral circumflex and perivesicular venous system was demonstrated. No collateral veins were seen bypassing the umbrella. A coagulation work-up including plasma fibrinogen concentration, platelet count, prothrombin time, thrombin time, and partial thromboplastin time was normal.

During the first 48 hours the edema and inflammatory reaction worsened. Fogarty catheters were inserted into both femoral veins (which were extremely inflamed and surrounded by fibrous tissue) and many large clots were removed from the iliac and femoral veins. At the conclusion of the procedure there was good back bleeding from the iliac veins. Postoperatively the edema did not change for 7 days, but rapid decrease in fluid and tenderness occurred during the next week.

Since it was felt that the patient's recurrent pulmonary emboli had probably come from above the prosthesis, an inferior vena cava ligation was performed just distal to the renal vein. At laparotomy the umbrella was found in the lower cava about 2½ in. below the right renal vein. It was firmly adherent to the wall of the vein and surrounding tissues and a large organized thrombus was visualized on the superior and inferior surface. The entire area was encased in fibrous tissue. The umbrella was not disturbed since its removal would have necessitated major dissection without benefit to the patient.

The patient continued to improve postoperatively, and at the time of discharge his edema was markedly decreased. He was advised to wear elastic support and to continue to take Coumadin.

Discussion

Interruption of flow through the inferior vena cava is often needed to terminate pulmonary embolism from the veins of the lower extremities and pelvis. In order to obviate the need for surgery, Mobin-Uddin and associates[1,2] introduced a fenestrated umbrella-shaped Teflon prosthesis that occludes the lower inferior vena cava. After its release from a catheter inserted through the internal jugular vein, the umbrella springs open and its prongs penetrate the walls of the vein. Mobin-Uddin[3] has reported favorable results in more than 100 patients. The manufacturer[4] has reported its use in more th... 50 patients

Table I Pulmonary complications of congenital heart disease

	Pulmonary complications	Cardiac lesion
Congenital		
	Agenesis lung or lobe	Dextrocardia[11] other[6]
	Hypoplasia	Scimitar syndrome[6]
	Absent pulmonary artery branch	Tetralogy[12] other
	Bronchiectasis	Kartagener's triad[3,11]
	Pulmonary arteriovenous fistula	Atrial septal defect[14]
	Sequestration other	Various anomalies including tricuspid atresia
Acquired		
	Infective[15]	
	Recurrent pneumonia	Left-to-right shunt in infancy
	Bacterial endocarditis lung abscess	
	Tuberculosis histoplasmosis	
	Noninfective	
	Bronchial artery enlargement	Extreme tetralogy[16,17] other[18,19]
	Other collaterals enlarged	Postoperative tetralogy[6]
	Pulmonary vascular obstructive disease (PVOD)	Eisenmenger reaction[1,2,18,21,22]
	Pulmonary venous engorgement	Mitral stenosis[1] Cor triatriatum[23]
	Pulmonary thromboembolism	Large left-to-right shunts
	Postoperative complications other	
	Atelectasis persistent or recurrent	Endocardial fibroelastosis[6]

Hemoptysis d e t these d so d s mph ed th re iew

Table II Pathophysiologic basis for hemoptysis in 42 cases

	Cause	No
Group I	*Extreme pulmonic stenosis (mostly tetralogy with outflow atresia)*	
	Enlarged bronchial arteries (usually associated with pulmonary thromboses of small vessels and with pulmonary arterial hypoplasia)	16
	Other collateral vessels	1
Group II	*Pulmonary vascular obstructive disease (PVOD)*	
	Primary pulmonary hypertension	1
	Eisenmenger reaction in left to-right shunt or single ventricle	4
	PVOD developing following systemic pulmonary anastomosis for tetralogy and so forth	
A	*Associated pregnancy or oral contraceptives*	10
Group III	*Other causes*	7
		3

to our attention during the past 3 or 4 years while we have been collecting data on pulmonary complications We have not attempted to assess the incidence of hemoptysis in the different malformations preferring to concentrate on the underlying pathophysiological mechanisms The preponderance of patients with tetralogies and extreme pulmonic stenosis in the series is due to the large number of such patients followed at The Johns Hopkins Hospital over the years in The Helen B Taussig Children's Cardiac Center many have been followed from infancy to adult life Patients with other types of malformations have either been transferred as they reached adolescence or have been followed by other physicians

Although there is some overlap the basis for the hemoptysis in the 42 cases can be conveniently classified into 3 major groups (Table II)

Review

Pulmonary complications of congenital heart disease: Hemoptysis

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Catherine A. Neill, M.D., F.R.C.P. (Lond.)
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The literature on pulmonary complications of congenital heart disease has primarily emphasized pulmonary vascular disease *in left to right shunts*[1-3] or the effects in infants of bronchial compression and obstruction due to cardiomegaly or dilated pulmonary artery branches.[4] A number of scattered reports have considered the syndromes of congenital cardiopulmonary anomalies[5,6] or the hemodynamic effects of hypoplasia or agenesis of a lung[7] or a pulmonary artery.[8,9]

The present review will attempt to delineate the major pulmonary complications encountered in a large population with congenital cardiac disease. An abbreviated classification of some of the more frequently encountered pulmonary complications is given in Table I.

Although each of the complications listed above may be encountered at any age, certain problems such as atelectasis and recurrent pulmonary infections are particularly prevalent in infancy, while others are rare before the second decade of life. *Hemoptysis*, one of the most dramatic and potentially lethal[4,25] of all cardiopulmonary complications, may be the presenting symptom of many forms of pulmonary involvement. This present review will emphasize hemoptysis due to acquired noninfective pulmonary complications of congenital heart disease indicated by an asterisk in Table I.

The most common causes of hemoptysis in the general population are chronic bronchitis and bronchiectasis, which together account for 20 per cent of cases. Unexplained hemoptysis is common, as illustrated in the series of Johnston and colleagues,[6] in which no cause was found in 44 per cent of 324 patients. Well recognized cardiovascular causes of hemoptysis include pulmonary embolism, mitral stenosis, congenital telangiectasis, and hypertension with intrabronchial leakage from an aneurysm.

Hemoptysis in congenital heart disease has been most frequently described in pulmonary vascular obstructive disease (PVOD) including Eisenmenger's complex,[1,2,23] but it is also known to occur in patients with enlarged bronchial circulation[15] or pulmonary venous congestion.[3]

The present review is based on 42 cases of hemoptysis in congenital heart disease representing all those seen by us or brought

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Hemoptysis				*Death and autopsy*	*Comment*
at onset	*Severity*¶	*Recurrence*	*Years survival after onset*		
18	+++	R	5	D A	Bronchials enlarged at autopsy apical cavitation Aspergillus super infection death following lobectomy
18	+	R	26+		Improved following central shunt at 40 years of age
18 (atemesi 6 years)	+++	R	2	D A	Autopsy showed multiple thrombi small pulmonary arteries bronchials enlarged
19	++	P	8+		OHS 20 year large hemoptysis week later no further recurrence good result
47	+	P	2	D A	Pulmonary osteoarthropathy death at attempted OHS
18	+++	R	2	D	Pulmonary osteoarthropathy death from massive hemoptysis right upper lobe
[illegible]	+++	R	17	D A	Died following attempted pulmonary valvotomy
?9	++		6+#		*OHS 29* years good result no further hemoptysis
?1	+		19	D A	One hemoptysis prior to shunt later developed [illegible]OD
[illegible]	+		12	D A	Died following attempted OHS autopsy revealed bronchial enlarged history systemic *thrombo-embolism*
??	+		9+		OHS ?3 year good result no further hemoptysis
20	+++	R	?	D	Massive hemoptysis from aneurysm right upper lobe 21 year shock cerebral damage death several months later
4	+++	R	?3	D A	Died following intrapulmonary hemorrhage at site of anastomosis subclavian to-bronchial vessel no right pulmonary artery or left pulmonary artery identified at *autopsy*‡‡
1?	++	R	6+		Intercostal pulmonary artery aneurysm (postsurgical)
23	+		6+		
2?	+	P	3+		Extreme cyanosis
11	+++	R	5 days	D	

Table III. Group I. Bronchial (collateral) vessels in extreme pulmonic stenosis

Case	Race and sex	Diagnosis*	RV outflow atresia	Shunt age(s)§	Ty pe ph s
1	WM	TOF	+†	12	RD
2	WM	TOF	+	21	LL
3	WM	TOF	+	40 7	PI
4	BM	TOF	+	4	
5	WF	TOF ASD	(+)‡		LL
6	WM	TOF	+ main pulmonary artery	17	
7	WF	TOF			
8	WF	TOF	(+)	28 13	(I) K
9	WF	TOF ASD	(+)	18 22	(I)
10	WF	TOF	+	13	
11	WM	TOF		10	
12	WM	TOF	+	7 21	L
13	WM	Truncus, Type IV	+	5	
14	WF	TOF	+	2	K(I)
15	WM	Tricuspid atresia	(+)	6 13 20	
16	WM	Ebstein ASD		20 Superior vena cava-Right pulmonary artery	
17	BM	Levocardia Situs inversus Cor biloculare Absent left pulmonary artery	+		

TOF = Tetralogy of Fallot; ASD = atrial septal defect.
† + = Complete atresia.
‡(+) = [illegible]
§Shunt age( ) at time [illegible]
‖RI = [illegible] present in [illegible] (I) = [illegible]
[illegible] + less than 5 [illegible] ++ 50 [illegible] +++ 100 [illegible] 500 [illegible]
¶Patient [illegible] still living at time of this report.
*OHS = Open heart surgery (total correction).
‡We are grateful to Dr. [illegible] Bernstein of [illegible] for [illegible] on this case.

Hemoptysis				Death and autopsy	Comment
e at onset	Severity¶	Recurrence	Years survival after onset		
18	+++	R	5	D A	Bronchials enlarged at autopsy apical cavitation Aspergillus super infection death following lobectomy
18	+	I	26+		Improved following central shunt at 40 years of age
18 (m teme 1 6 years)	+++	I	2	D A	Autopsy showed multiple thrombi small pulmonary arteries bronchials enlarged
19	++	R	8+		OHS 20 years large hemoptysis week later no further recurrence good result
47	+	I	2	D A	Pulmonary osteoarthropathy death at attempted OHS
18	+++	I	2	D	Pulmonary osteoarthropathy death from massive hemoptysis right upper lobe
0	+++	R	17	D A	Died following attempted pulmonary valvotomy
?9	++		6+#		OHS ?9 years good result no further hemoptysis
?1	+		19	D A	One hemoptysis prior to shunt later developed PVOD
1	+		12	D A	Died following attempted OHS autopsy revealed bronchials enlarged h tory systemic thromboemboli m
?2	+		9+		OHS ?3 years good result no further hemoptysis
20	+++	R	2	D	Massive hemoptysis from aneurysm right upper lobe 21 years shock cerebral damage death several months later
4	+++	I	?3	D A	Died following intrapulmonary hemorrhage at site of anastomosis subclavian to-bronchial vessel no right pulmonary artery or left pulmonary artery identified at autopsy*‡
12	++	R	6+		Intercostal pulmonary artery aneurysm (postsurgical)
?3	+		6+		
2?	+	I	3+		Extreme cyanosis
11	+++	R	5 days	D	

Group I Extreme pulmonic stenosis

The 17 patients in this group all had extreme right ventricular outflow obstruction. Many of those listed as tetralogy (tetralogy of Fallot [TOF] in Table III) had complete atresia of the right ventricular outflow tract. In some this atresia was of congenital origin and associated with absence or extreme hypoplasia of the main pulmonary artery, while in others the atresia was almost certainly of the acquired type previously described by our group.[29] Some authors list such patients as having pulmonary atresia with ventricular septal defect' or occasionally 'pseudotruncus.' They are, however, extreme examples of tetralogy of Fallot or, embryologically, of marked conal hypoplasia. This group forms an unusual and probably unique series in that most of the patients were able to survive to 20 or more years of age despite marked cyanosis, in part due to compensatory bronchial circulation, and in part due to surgical creation of one or more systemic pulmonary anastomoses. The large majority of these anastomoses were Blalock-Taussig shunts or anastomoses between the subclavian and pulmonary arteries (Table III). The anatomic diagnosis in all cases listed in Table III was confirmed by catheterization and angiocardiography and in most at subsequent open heart surgery or autopsy. The age of onset of hemoptysis varied from 4 to 47 years and in most cases occurred from the lung with the less adequate pulmonary flow, namely the lung supplied by bronchial vessels.

The pulmonary vascular bed. A variety of methods has been used to study the pulmonary vascular bed in extreme pulmonary stenosis or atresia, including whole lung section, serial lung sections, postmortem angiography,[17] or bronchial arteriography,[17,19] and lung biopsy.[30] Detailed reviews of the techniques and findings are available in Cudkowicz's[17] excellent monograph and in other texts.[18,31,8] Three major changes have been defined, namely, thrombosis in the small pulmonary vessels (often associated with intimal fibrosis), increased size and tortuosity of the bronchial arteries, and relative hypoplasia of the pulmonary arterial walls. All 3 changes may contribute to hemoptysis and not infrequently may interact. For example, *hypoplasia of the pulmonary arterial wall* may predispose to aneurysmal dilatation and rupture; such a sequence of events has been recorded in pulmonary arterial stenosis with aneurysmal poststenotic dilatation.[33] One patient in our series (Case 12, Table III) with tetralogy of Fallot and right ventricular outflow atresia was noted to have marked hypoplasia of the right pulmonary artery when a subclavian pulmonary anastomosis was performed at 7 years of age. He developed progressive aneurysmal dilatation of the upper lobe artery over the years (Fig. 1, *A* and *B*), had his first hemoptysis at 20 years of age, and died of complications following a massive hemoptysis from the angioma of his right upper lobe at age 21. The angioma appeared on angiography to be composed of a direct communication between a large systemic (?bronchial) artery and the very hypoplastic right upper lobe branch of the pulmonary artery (Fig. 1, Case 12).

Pulmonary thrombosis. Thrombosis affecting the small pulmonary arteries in patients with severe pulmonary stenosis was first described by Rich.[34] Ferencz[8] noted these lesions to be more widespread and severe in patients with cyanotic spells and observed regression in these thrombotic lesions following establishment of a more adequate pulmonary blood flow after a shunt procedure.[35]

Although polycythemia and the possible attendant disorders of the clotting mechanism may contribute to in situ thromboses, the pathologic studies of Best and Heath[37] and Ferencz[8] showed no clear correlation between severity of thrombosis and hematocrit levels. Naeye, Kisseroff, and Jacobson[38] produced thrombotic lesions in the small pulmonary arteries of 2 dogs by markedly reducing pulmonary flow to one lung without inducing polycythemia. The evidence is thus that decreased flow in the pulmonary arteries is the main factor producing in situ thrombosis.

In the present series, pulmonary thrombosis in the small vessels was found at autopsy in 4 of the 7 autopsied cases. Fourteen of the 17 patients had a history of cyanotic spells in infancy, all had extreme reduction in pulmonary blood flow, and most were at least 10 years of age before



Fig 1 A and B Case 12 angioma and fine reticular marking of bronchial circulation A Age 6 years Lung fields clear B Age 20 years Arrow indicates angiomatoid lesion in upper pole of the right hilum



Fig 1C Arteriogram of Case 12 Catheter tip in innominate artery Upper arrow indicates round angiomatoid lesion supplied by systemic (?) bronchial artery to right upper lobe communicating with the right subclavian artery Lower arrow indicates subclavian pulmonary artery end to-end anastomosis

any palliative surgery was undertaken Thus all had multiple predisposing factors to in situ pulmonary thromboses Thrombi may have been important in patients such as Case 4 (Table III) with severe cyanosis over many years despite a shunt procedure hemoptysis at 19 years of age and an eventual good result from open heart surgery

Enlarged bronchial circulation This is thought to be the major cause of hemoptysis in patients with decreased pulmonary arterial flow Bronchial artery changes have been documented pathologically in many studies[16 39] and some of the clinical and radiologic manifestations have been described[28 40] Physiologic studies have shown increased bronchial flow in tetralogy of Fallot ranging from 0 14 to 2 8 L /min /M[2 41 42]

Although anatomic classifications of the bronchial arteries are available[17 44] data are lacking on precisely which bronchial vessels enlarge in extreme pulmonic stenosis and on the rate of enlargement with age Pathologic studies by Collister[16] and others suggest that most collateral vessels arise in the hilum but surgical findings frequently indicate massively enlarged pleural collaterals Hales and Liebow[39] have shown in postmortem studies that bronchial arteries near the hilum may dilate in infancy or even in intrauterine life and supply the pulmonary vessels by retrograde flow

In the present series x ray or fluoroscopic findings indicative of enlarged bronchial arteries were present in 8 of the 17 patients (Fig 2) and dilated bronchials were described at operation or autopsy in 13 Finger clubbing which was thought to

Group I Extreme pulmonic stenosis

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Fig 3 *A* and *B* Case 6 enlarged bronchial filling of pulmonary artery branches A Right ventricular angiocardiogram revealing pulmonary outflow atresia *B* Selective bronchial arteriogram showing right and left pulmonary arteries fill from bronchial artery No filling of main pulmonary artery or right upper lobe branch (Catheter tip in bronchial artery)

be a sign of increased bronchial flow [4] was present in all and pulmonary osteoarthropathy was a major symptom in 2 of the group Bronchial arteriography [46,47] in vivo in Case 6 showed a dilated bronchial artery entering the left pulmonary artery near its origin and filling both right and left pulmonary arteries by retrograde flow (Fig 3 *B*) There was no filling of the atretic main pulmonary artery or of the right upper lobe branch Massive hemoptysis in the right upper lobe supplied entirely by bronchial vessels was the cause of this boy s death and was attributed to probable rupture of an enlarged bronchial artery analogous to that seen on the left side but without any communication to a true pulmonary vessel Massive bleeding in this series as previously noted usually occurred from the lung or lobe with the least adequate pulmonary blood supply For example in Case 17 massive fatal hemoptysis occurred in the left lung with complete absence of a left pulmonary artery Massive hemoptysis has been recorded as a major symptom at a relatively young age in the absence of one pulmonary artery without other associated heart disease and has in such cases also been attributed to bronchial artery rupture [9]

Radiologic progression The fine reticular pulmonary markings and other stigmas of increased bronchial flow have been described previously [40] Review of the 17 cases summarized in Table III showed that prior to and accompanying the onset of hemoptysis an interesting series of clinical pathologic and radiologic changes may occur The radiologic changes are best seen in the upper lobes (Figs 2 4 5 6 7) and simulate chronic tuberculosis or histoplasmosis The term pseudofibrosis seems most appropriate We attribute the radiologic appearance to the late effects of a series of small pulmonary artery thromboses and infarctions associated with localized pleuritis resulting in apical pleural capping The dilated bronchial arteries themselves probably play a role in forming the radiologic picture The changes are more readily seen in lordotic views [43] Pseudofibrosis was seen in 9 patients of this group all over 15 years of age In 2 patients the first hemoptysis preceded the abnormal radiologic appearance while in others both appeared virtually simultaneously resulting in much diagnostic difficulty Case 2 is of particular interest in that despite extensive pseudofibrosis (Fig 2) pulmonary function studies showed only a moderate degree of restriction and a slight degree of obstructive ventilatory defect The vital capacity was 71 per cent of predicted and a diffusion capacity was normal This was interpreted to mean that despite the radiologic changes further surgery might be tolerated At the age of 40 despite the presence of severe pseudofibrosis and a history of recurrent small hemoptyses for 22 years the patient underwent a central



Fig. 2. *A* through *E*, Case 2, enlarged bronchial and pseudofibrosis. *A*, Age 21 years. Lungs show fine reticular pattern bronchial circulation. *B*, Age 34 years. Tomogram reveal apical capping, pseudo-fibrosis, and cystic areas in upper lobes. *C*, Age 34 years. Angiogram shows multiple tortuous vessel (probably bronchial arteries) in upper lobe. Aorta fills from right ventricle. Main pulmonary artery not visualized. *D*, Age 38 years. Pleural capping and cystic areas. Compare with *A* and *B*. *E*, Age 42 year. Barium swallow shows irregular indentation of esophagus by collaterals. (Relevant area between 2 black lines.)



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Table IV Hemoptysis and pseudofibrosis

Severe cyanotic heart disease
Survival for 15 or more years
Reduced or absent pulmonary artery flow
Enlarged bronchial artery circulation
Apical pseudofibrosis
Cavitary changes may be followed by secondary opportunistic infection

Examination showed a cyanotic boy with a hemoglobin of 24 Gm and hematocrit of 83 No cardiac murmurs were present. On fluoroscopy the aorta was observed to be large and the pulmonary conus extremely concave A pulmonary artery was visible on either side but in addition there were many smaller vessels at both hilar areas extending almost to the periphery which were thought to be collateral vessels The electrocardiogram (ECG) showed right axis deviation and right ventricular hypertrophy

Angiocardiography showed early filling of the aorta from the right ventricle and no direct flow into the pulmonary arteries but hilar collateral vessels were visualized This confirmed the clinical impression of pulmonary outflow atresia the pulmonary arteries were thought to be patent distally as judged by their size on x ray and by evidence of filling on angiocardiography At operation in 1948 Dr Blalock noted many collateral vessels in the mediastinum and found a small quiet left pulmonary artery A collateral which entered it far proximally was torn and a good deal of bleeding occurred A left end to-end subclavian pulmonary anastomosis was performed

The patient tolerated the procedure well and developed a good continuous murmur Postoperatively the hematocrit dropped from 83 to 63 the hemoglobin from 24 to 20 Gm and the arterial saturation rose from 64 to 7? per cent

He returned 10 years later in 1958 at the age of ? For about 6 years postoperatively cyanosis had been much less with an increase in exercise tolerance and rate of growth However for the past 4 years cyanosis had increased and the patient became more limited and began to have recurrent hemoptyses He had had a work up in a sanatorium for tuberculosis this diagnosis was excluded.

Examination showed a continuous murmur of Grade 1 to 2 intensity over the left upper chest an ejection click and a loud single second sound Breath sounds were impaired over the right upper lung field with amphoric breathing and posttussive râles The hemoglobin was 20 Gm. and the hematocrit 60

Review of the chest x rays showed that in 1948 there were no parenchymal lesions By 1955 the film taken in the sanatorium showed a moderately extensive "fibrotic appearing infiltrate in the right upper lobe with probable cavitation By 1958 x ray and tomography showed many cavities containing inspissated material Angiocardiography (Fig 6) was repeated and again showed right ventricular outflow atresia The right pulmonary artery was visualized very late while the left was visualized



Fig 6 Case 1 pseudofibrosis and opportunistic infection Aspergillus Age 22 years Venous angiocardiogram reveals atresia of the right ventricular outflow tract. The left pulmonary artery fills from the aorta via an end to-end subclavian pulmonary anastomosis Right pulmonary artery not visualized Bilateral upper lobe infiltrates are extensive and cystic on right

shortly after the aorta confirming that the subclavian pulmonary anastomosis was still functioning The opacification of the right apex was thought to be due to crowding of vessels in an area of consolidation. Cardiac catheterization confirmed the presence of a ventricular septal defect and systemic levels of right ventricular pressure

Following discharge back to his home in Wisconsin the patient continued to have hemoptysis at one time he lost a pint of blood very rapidly A right upper lobectomy was done The lobe was found to be contracted to about one third of normal size and completely fixed to the chest wall There was severe bleeding and a large amount of collateral circulation Cystic lesions containing dense hemorrhagic and necrotic material were found from which Aspergillus was cultured The patient developed postoperative pleural infection necessitating open drainage and died some days later

Autopsy confirmed the presence of ventricular septal defect with complete occlusion of the pulmonary artery at its origin and hypoplasia of the main pulmonary artery Lung sections showed some thromboses in the small pulmonary artery branches

The pathology findings are summarized in a letter from Dr Lawrence T Giles of Madison Wisconsin

The lesion in the right upper lobe was an angiomatous one with numerous connections between the costal and bronchial arteries some of which appeared aneurysmal There were large cystic areas filled with Aspergillus Dr Helen Dickie s view was that there were preformed cavitary areas which then became occluded with Aspergillus The main problem was failure of pulmonary artery blood supply to the

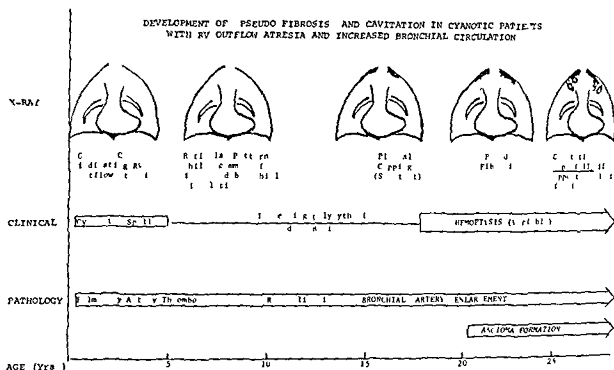


Fig 4 Sequence of events in pseudofibrosis Diagram of clinical pathologic and radiologic progression in hemoptysis and pseudofibrosis (We acknowledge the aid of Dr Willis Hurst in the preparation of this diagram)

A B

Fig 5 *A* and *B* Case 3 *A* Age 8 years Lung fields are clear *B* Age 19 years Bilateral apical pseudofibrosis is present Inset right apicogram

ascending aorta to right pulmonary artery shunt with striking improvement in cyanosis and polycythemia Hemoptyses have persisted, but to a lesser degree in the subsequent 4 years Similar respiratory function findings, namely, a normal diffusing capacity and a slight reduction in vital capacity and forced expiratory volume per 1 second (FEV_1), not improved by Isuprel have been observed in a few other subjects

In this patient and 7 others with pseudofibrosis, all studies were negative for tuberculosis, histoplasmosis and other granulomatous infections Nevertheless in advanced cases fibrosis may be associated with angiomatous cavitation and with secondary opportunistic infection[49] with Aspergillus or other organism Such a case is described in detail below The presumed sequence of pathologic and radiologic changes in pseudofibrosis is outlined in Fig 4 and summarized in Table IV

Case 1 S R was first seen in 1948 at 12 years of age with a history of frequent cyanotic spells in infancy and constant cyanosis from 6 months of age

ght lung which was supplied by bronchial and intercostal arteries The episodes of pulmonary bleeding were from the angiomatous lesions formed by these vessels

DISCUSSION Hemoptysis in enlarged bronchial arteries may occur from erosion of a tortuous dilated varicose bronchial artery directly into a bronchus[41] from localized pulmonary infarction at the bronchopulmonary anastomotic site or from rupture of an atherosclerotic bronchial artery plaque[5] Massive hemoptysis or intrapulmonary bleeding with bronchial artery rupture was the immediate cause of death in Cases 6 13 and 17 in the present series and was a major contributing cause of death in Cases 1 and 12

Other collateral vessels Hemoptysis is frequent in congenital pulmonary arteriovenous fistula[32] It may also occur in association with aberrant vessels from the descending aorta supplying a sequestered pulmonary lobe[43] or in systemic pulmonary arteriovenous fistula[54,55] An unusual type of systemic pulmonary arteriovenous fistula causing hemoptysis is described below

Case 14 B H was first seen at 10 months of age with a history of cyanosis dating from 3 months of age A Grade 2 systolic murmur was audible down the left sternal border X ray showed a markedly concave pulmonary conus and a diagnosis of tetralogy of Fallot was made (Fig 7) She developed severe cyanotic spells and by two years of age her hemoglobin was 17 8 Gm hematocrit 75 At operation a left end to-end subclavian pulmonary artery anastomosis performed by Dr Blalock an incision was made in the third left intercostal space Many collateral vessels were noted in the chest wall and mediastinum the left pulmonary artery was small about 6 mm in diameter and of low pressure

Over the next few years the child did moderately well although polycythemia increased slowly The lung fields were noted to show an unusual reticular pattern suggesting increased bronchial flow and the vascularity of the left lung was greater than that of the right

At 12 years of age she had a sudden hemoptysis of bright red blood lasting for 2 days occurring in 2 episodes each amounting to approximately half a teacup Two days later a patchy infiltrate was noted in the middle third of the left lung periphery and was attributed to a small infarct although a lung scan did not show any area of decreased uptake

Three years later the patient was admitted with a history of three episodes of hemoptysis amounting to about 50 to 75 c c The sudden onset followed a class trip to Washington with more than usual activity and excitement There had been no associated chills or fever During the 10 days after admission there were 5 gross hemoptyses of between 50 to 150 c c of bright red blood X ray (Fig 7 B) showed a left midlung opacity Emergency lobectomy was being considered when the episode subsided Skin tests for tuberculosis and fungal infections were consistently negative as were sputum cultures Bronchoscopy showed blood to be issuing from the left upper lobe orifice

Selective right ventricular angiography showed a hypertrophied right ventricle a narrow infundibulum with atresia of the pulmonary outflow tract a large right aortic arch and a functioning left end to-end Blalock Taussig anastomosis (Fig 7 C) An enlarged and hypertrophied highest intercostal artery arising at the level of T4 and supplying the upper 4 left intercostal spaces was noted The fourth intercostal artery was markedly elongated tortuous and dilated with associated rib notching The vessel appeared to be the principal contributor to a large mass of angiomatoid vessels in the lateral aspect of the left lung (Fig 7 D) which then drained via the left pulmonary veins to the left atrium (Fig 7 E) The angiomatoid malformation was noted to correspond to the surgical entry site

Over the ensuing 3 years the patient has remained clinically stable and no further hemoptyses have occurred

DISCUSSION If the subclavian artery is used to perform a systemic pulmonary anastomosis various secondary vascular changes may occur including dilatation of intercostal vessels great enough to produce unilateral rib notching[56] or the rare late development of a subclavian steal syndrome[57] The degree of rib notching in the patient mentioned above was unusually striking and correlated with the extreme degree of intercostal artery enlargement resulting in a unique type of systemic pulmonary arteriovenous fistula This complication was not otherwise encountered to our knowledge in the almost 2 000 patients who have undergone Blalock Taussig anastomoses in this institution

This patient illustrates well the therapeutic dilemma sometimes encountered in the acute phase of hemoptysis in cyanotic patients since lobectomy or pneumonectomy in this case would have resulted in the removal of the only efficient oxygenating lung

Group II Pulmonary vascular obstructive disease (PVOD)

Hemoptysis has long been recognized as one of the cardinal symptoms of severe pulmonary hypertensive vascular disease[12] The incidence appears to rise sharply in the second decade of life being rare under 10 years of age[53]

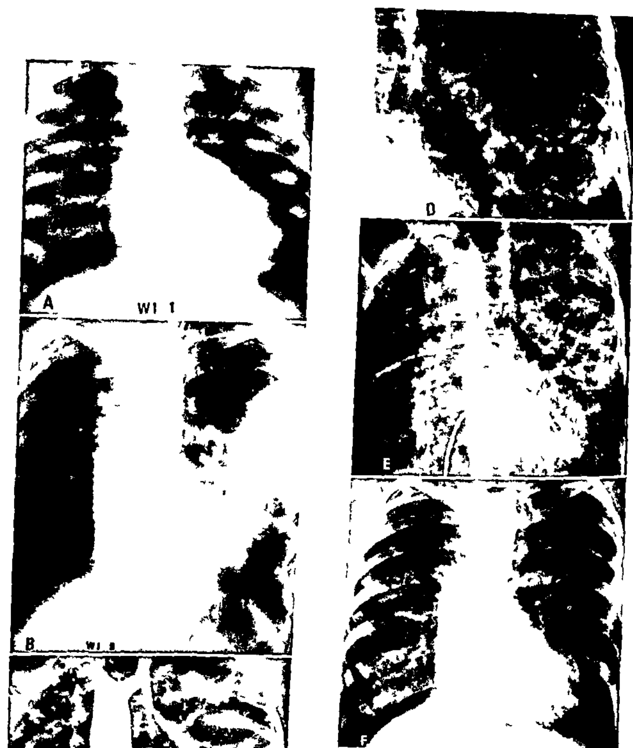


Fig. 7. *A* through *F*, Case 14, intercostal pulmonary artery aneurysm following shunt for tetralogy. *A*, Age 18 months. Lung fields are clear. *B*, Age 15 years, during hemoptysis. Left midlung opacity and right apical pseudofibrosis. *C*, Right ventricular angiocardiogram showing atretic pulmonary outflow tract. Left lung filling from end-to-end subclavian pulmonary anastomosis. Note rib notching on left. Arrow indicates angiomatous lesion. *D*, Angiocardiogram close-up revealing intercostal artery supplying angioma. *E*, Angiocardiogram levophase showing angioma supplied by intercostal artery and draining into pulmonary veins. *F*, Ten days after hemoptysis. Lung fields almost clear.

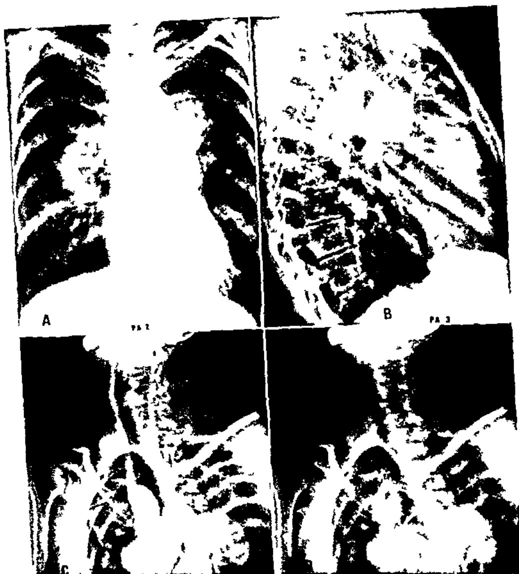


Fig 8 A through D Case 23 PVOD following shunt for tetralogy A Age 24 years Marked dilatation of right and left pulmonary arteries with decreased peripheral vascularity i e pruning effect B Lateral view Dilated pulmonary arteries frequently mistaken for enlarged hilar nodes C Aortogram left anterior oblique view reveals markedly dilated right subclavian artery anastomosing with pulmonary artery D Later view showing capillary enlargement a possible source of hemoptysis

pulmonary anastomotic procedure for tetralogy or for other cyanotic malformations originally associated with pulmonic stenosis[21,51] The incidence of PVOD following such an anastomosis has been recently found by Dr Taussig to be approximately 7 per cent over a 20 year period The large number of such patients in the present paper should not be taken to mean that this is a common complication of shunt procedures but rather that when it does occur hemoptysis is a frequent manifestation The radiologic and angiocardiographic findings in Case 23 of PVOD following a shunt procedure are illustrated in Fig 8 Case 9 (Table III) in which the clinical and pathologic findings have been reported by Folger and Otken[55] is of interest in that the only recorded hemoptysis occurred when the patient was 21 years of age before any cardiac surgery It seems probable that the patient had many intrapulmonary

Table V. Group II. Pulmonary vascular obstructive disease (PVOD)

Case	Race and sex	Diagnosis	Shunt age	Hemoptysis: Age at onset	Hemoptysis: Severity	Hemoptysis: Recurrence	Hemoptysis: Years survival after onset	Death and autopsy	Comment
18	WF	Primary pulmonary Hypertension PFO		12	+	R	2+		
19	WM	VSD (Eisenmenger's)		27	+	R	12+		
20	WM	VSD (Eisenmenger's)		14	++	R	2+		Male sibling died of primary pulmonary hypertension (autopsy)
21	WF	Single ventricle with transposition		21	+	R	3+		
22	WM	Single ventricle with transposition		18	++		5	D A	Pulmonary thrombosis atherosclerosis
		PVOD following systemic pulmonary anastomosis							
23	WF	TOF	6	24	+++	R	4+		
24	WM	TOF	16	32	+		6+		
25	WM	TOF	27	33	+++	R	6	D A	Hemoptysis recurrent until death from cerebral embolism thickened pulmonary vessels at autopsy
26	WM	TOF	12 (Potts)	27	+++	R	6+		
27	WM	TOF	15	30	+++	R	8+		
28	WM	TOF	13 18	24	+++		9+		
29	WF	TOF	16 26	26	+		8	D A	Died following attempted OH; pulmonary atherosclerosis at autopsy
30	WM	TOF	4	19	+	R	8+		
31	WM	TOF	7	19	++	R	2	D A	Death due to dissecting aneurysm of pulmonary artery pulmonary atherosclerosis
32	WM	Dextrocardia single ventricle pulmonary stenosis	10	15	+		17+		

PFO = Patent foramen ovale VSD = Ventricular septal defect Other abbreviations as in Table III

The *pathologic basis* for hemoptysis in pulmonary vascular obstructive disease has been well defined.[1] An excellent diagram of the development of the dilatation lesion of the pulmonary arteriolar wall is available in Harris and Heath's monograph.[3] Small repeated hemoptyses can readily be visualized as occurring from the Grade V dilatation lesions typical of advanced pulmonary hypertension. Despite much study there is still some doubt as to whether these dilatation or angiomatoid lesions represent outgrowth of the small pulmonary arteries or dilated, degenerating bronchial arteries. Whichever theory is correct, the pathologic findings correlate well with the clinical nature of the hemoptyses, which are usually mild or moderate in degree and recur at unpredictable intervals. Clarkson[68] found hemoptysis a bad prognostic sign in patients with ventricular septal defect and PVOD since 7 of 11 patients or 64 per cent survived less than 7 years after the onset of this complication.

In our series the anatomic diagnosis in all 15 patients in Group II was confirmed at one or more cardiac catheterizations (Table V). Hemoptysis first occurred between 12 and 34 years of age (mean 22 years) and recurred in 10 of the 15. The series is unusual in that PVOD in 10 patients appeared as a late complication following a systemic



Fig. 9. A and B. Case 33 PVOD (Eisenmenger) hemoptysis during pregnancy. A, Age 24 years during hemoptysis. Pulmonary artery lordotic view. Collapse of the left upper lobe and shifting midline structures. Herniation of the right lung into the left upper hemithorax and accompanying infiltration. Tenting of left side of the diaphragm. B, Ten days later the lung fields have cleared.

pulmonary thromboembolism in adult cyanotic patients with PVOD the exact relationship of the medication to outcome is difficult to elucidate. For example, the age at death and the autopsy findings were very similar in Case 21 (Table V), a male, and in Case 36, a female who developed massive pulmonary thromboembolism while taking oral contraceptives. A detailed analysis of the problem in cardiac patients is necessary, but at present both pregnancy and oral contraceptives appear to carry a significantly greater risk of pulmonary thromboembolism in women with PVOD than in the normal population.

Case 33. K. M. was first seen at 7 weeks of age with a history of a cardiac murmur from one month of age. She was poorly nourished and had a harsh precordial systolic murmur. By 5 months of age the murmur persisted and some hepatomegaly was noted; the patient was digitalized. The heart on fluoroscopy was markedly enlarged with a full pulmonary artery. K. M. improved in the second year of life. A harsh systolic murmur and thrill persisted down the left sternal border. The physical signs were always thought to be somewhat atypical for a ventricular septal defect since the diagnosis was not confidently made.

By 9 years of age K. M. was acyanotic and very active. At that time there was no thrill and only a Grade 1 to 2 blowing systolic murmur. Heart size on x-ray was normal although the pulmonary vascularity was still increased centrally. The ECG previously not remarkable showed marked right ventricular hypertrophy. During the patient's early teens slight but definite cyanosis became apparent. Cardiac catheterization in 1959 at the age of 16 years showed a pulmonary artery pressure of 135/73 mm Hg, a femoral artery pressure of 114/72 mm Hg, and an arterial oxygen saturation of 88 per cent. A right-to-left shunt was detected by dye curves at the ventricular level but no left-to-right shunt.

K. M. married at age 21 and about one year later had the first hemoptysis. It amounted to only one teaspoon of bright red blood with no obvious precipitating cause. She was found to be 2 months pregnant. The following day a small infiltrate was seen in the left upper lobe not visible on films taken 24 hours previously. She had a spontaneous abortion about 2 weeks later. No further hemoptysis or increase in symptoms occurred until 9 months later, about 11 weeks into her second pregnancy, when she had several small hemoptyses. She was hospitalized and while in the hospital she had several episodes of severe chest pain and repeated small hemoptyses (Fig. 9). A lung scan showed multiple areas of decreased uptake in both lung fields thought to be consistent with multiple areas of pulmonary embolism.

Hysterotomy and bilateral salpingectomy were performed. There was no evidence of any pelvic vascular or inflammatory disease. She had a benign postoperative course and was kept on anticoagulants for 6 months. In the ensuing 3 years she has remained well, has had no further hemoptyses and no decrease in exercise tolerance and has adopted a child.

COMMENT. This patient's hemoptysis seemed clearly related to hormonal changes induced by pregnancy since hemoptysis occurred only during pregnancy and stopped

Table VI. Group II-A. Hemoptysis associated with pregnancy or oral contraceptives

Case	Diagnosis	Hemoptysis			Comment
		Age at onset	Years survival after onset	Relation of pregnancy or contraceptive	
33	VSD PVOD (Eisenmenger's)	23	4+	10 weeks pregnant 10 weeks pregnant	First pregnancy terminated by spontaneous abortion about 12 weeks; second pregnancy therapeutic abortion for hemoptysis (see text)
34	Aortic pulmonary window PVOD	21	2+	3 months pregnant 8 months pregnant	First pregnancy spontaneous abortion; second pregnancy several small hemoptyses; prolonged bed rest; live-born child
35	Truncus Int. aortic arch PVOD	21	2+	Varying hormones for metrorrhagia for 4 years	Three mild recurrences in year since discontinuing hormones
36	TOF PVOD following shunt	24	1 month	5 months after starting pill	Died one month after onset; autopsy showed pulmonary thromboembolism and atherosclerosis
37	TOF PVOD following shunt OHS	34	4+	21 months after start pill 10 weeks pregnant	Had 4 successful pregnancies, two spontaneous abortions prior to starting pill; no major hemoptysis after stopping pill until tenth week of seventh pregnancy (spontaneous abortion)
38	TOF (Post OHS) no evidence PVOD	21	3+	6 months after starting pill	One mild recurrence 2 years after stopping pill during episode of flu
39	TOF shunt 13 years no no evidence PVOD	35	1+	4½ months after starting pill	Lung scan showed multiple pulmonary emboli; no recurrence 1 year after stopping pill

thromboses predisposing to the ultimate development of pulmonary hypertension and pulmonary thromboembolism.

Group II-A. Hemoptysis associated with pregnancy or oral contraceptives

Hemoptysis in 7 white women in the series (Table VI) appeared temporally and causally related to pregnancy or the use of oral contraceptives. 5 were cyanotic and had PVOD confirmed at one or more catheterizations. The sixth had had a successful total correction for tetralogy but had been cyanotic till about 18 years of age. She did not have PVOD. The seventh woman had a functioning Blalock-Taussig anastomosis and also did not have PVOD.

The Mayo Clinic group in a recent paper[58] reported that in 23 female patients over 16 years of age with Eisenmenger's complex, one had an uncomplicated pregnancy and another had "infrequent hemoptyses during both of two pregnancies." The overall hazard of pregnancy in Eisenmenger's complex is not yet clear from the literature, but the major risk does seem to be pulmonary thromboembolism.

The "thrombogenic" effects of both pregnancy and oral contraceptives continue to be much studied. A recent analysis of the available literature[60] assesses the risk of major thromboembolism in a women taking oral contraceptives to be between 4 and 8 times that of a control.

Oakley and Somerville[10] reported a rapid downhill course in 3 patients with PVOD while on oral contraceptives: one developed inoperable pulmonary hypertension in a previously operable ventricular septal defect. One with a complex cardiac malformation died of hemoptysis while the third showed a striking increase in effort intolerance and developed splinter hemorrhages in the hand. These authors make the interesting suggestion that oral contraceptives may at least in some cases cause an acceleration of the otherwise more slowly progressive disease of pulmonary vascular obstruction. Pregnancy seems to have had a similar effect in our Case 33 described in detail below.

Because of the tendency to spontaneous

earliest possible corrective surgery Frequent small hemoptyses in patients with pulmonic stenosis are probably associated with pulmonary thromboses in the small pulmonary arteries and are not necessarily a contraindication to corrective cardiac surgery as indicated by successful postoperative course in several patients in this series

The management of hemoptysis in PVOD may include venesections as a prophylactic measure and the usual techniques of reassurance supression of cough and so forth once hemoptysis does occur

Summary

Hemoptysis is reviewed as a rare but major complication of congenital heart disease Forty two patients with hemoptyses not associated with endocarditis tuberculosis or immediate postoperative complications are reviewed all but 2 were cyanotic

Group I (17 patients) had extreme pulmonic stenosis or atresia and hemoptysis was attributed to a combination of hemorrhage from enlarged tortuous bronchial arteries and thrombotic lesions in the small pulmonary arteries one patient bled from a postoperative intercostal pulmonary artery aneurysm In 9 patients all over 15 years of age hemoptysis was associated with pseudofibrosis at the lung apices The radiologic progression of this lesion not previously described is outlined

Group II (15 patients) had pulmonary vascular obstructive disease associated with varied intracardiac lesions In 7 additional patients all but two with PVOD hemoptysis was associated with pregnancy or oral contraceptives

The 3 patients in Group III had varying causes for hemoptysis including erosion of a large aberrant vessel to the lung following bronchoscopy

The relevant literature is discussed and the use of newer techniques in investigating the pulmonary vascular bed in vivo is emphasized

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Table VII Group III Hemoptysis from other causes

Case	Race and sex	Diagnosis	Hemoptysis				Death and autopsy	Comment
			Age at onset	Severity	Recurrence	Years survival after onset		
40	WF	Truncus Type II atelectasis left lower lobe due to arterial compression	5	+++		4	D A	Massive hemoptysis 24 hours following bronchoscopy no recurrence death due to congestive failure
41	WM	Pulmonary valvular stenosis (valvotomy at 7 years) acyanotic	19	+	R	[illegible]	D A	Death attributed to pulmonary edema associated with heroin addiction cause of hemoptysis uncertain
42	WM	VSD anomaly of right ventricle muscle bundle (OHS 16 years)	16	+		6 months +		Hemoptysis was presenting symptom postpericardiotomy syndrome

abruptly with either spontaneous or therapeutic abortion

Group III Other causes of hemoptysis

Pulmonary venous congestion on the basis of a congenital defect may lead to hemoptysis in patients surviving into adult life[12, 3]

In 3 cases in our series hemoptysis could not be attributed to collateral vessels, extreme pulmonary arterial hypoplasia or PVOD In one child of 5 years of age a single massive hemoptysis followed bronchoscopy, the presumed cause was erosion of the bronchial wall compressed by the overlying dilated left pulmonary artery (Table VII Case 40)

In Case 41 no cause was found for repeated small hemoptyses occurring for many years after successful pulmonary valvotomy Wagenvoort and colleagues[30] have commented on the marked vascular changes in the lungs in pulmonary stenosis with intact ventricular septum and it is possible that the bleeding in this patient was from persisting dilated bronchial vessels The patient eventually died suddenly from pulmonary edema associated with heroin addiction[62] In the third patient hemoptysis was the presenting symptom of a postpericardiotomy syndrome and occurred about 3 or 4 weeks postoperatively He made a good recovery and the symptom has not recurred

Discussion

Hemoptysis in the present series was seen almost exclusively in cyanotic patients and involved either bronchial or pulmonary arterial vessels Hemoptysis due to pulmonary venous engorgement has been reported, but was not seen in our series

As more cyanotic malformations become amenable to corrective surgery in early life it is probable that progressively fewer cyanotic adolescents and young adults will be seen and bleeding from dilated bronchial vessels an example of a disordered compensatory mechanism may hopefully disappear We hope that the present paper will stimulate further study of such patients by the techniques of tomography,[50] selective bronchial arteriography[46 47] or radioisotope scanning[61] Such studies seem promising in the elucidation of the natural history of prolonged decrease in pulmonary blood flow Investigation of patients with 'pseudofibrosis' has shown only a rare instance of secondary 'opportunistic' infection In most cases negative skin tests, sputum cultures and viral studies suggest that the underlying etiology is vascular, as outlined in Fig 4

The management of hemoptysis may present special problems if the affected lung is the major source of oxygenated blood Massive hemoptysis may well indicate rupture of a dilated bronchial artery and is an indication for detailed study and the

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cated RBBB was defined according to criteria of the New York Heart Association[10] with the QRS duration 0 12 sec or greater in Lead V_1 Partial bilateral BBB was diagnosed when left anterior hemiblock or left posterior hemiblock was present in addition to RBBB Other ECG evidence of bilateral BBB[7] occurred too seldom to allow statistical analysis Hemiblocks were defined according to the criteria of Rosenbaum[11] Left anterior hemiblock (LAH) shows left axis deviation of −45 degrees or greater associated with characteristic rS complexes in Leads II and III Left posterior hemiblock (LPH) shows right axis deviation of +120 degrees or greater an S1Q3 pattern and tall R waves in Leads II and III Previous evidence of right ventricular hypertrophy a vertical electrical axis (> +60 degrees) or extensive lateral myocardial infarction negates the diagnosis of LPH Only typical cases were included in this study with emphasis on the changes observed in serial records

Myocardial infarction was presumed to have occurred when the development of pathologic Q waves in the ECG accompanied a characteristic clinical presentation and rise in serum enzymes The ECG diagnosis of anteroseptal infarction was made when Q waves of 0 04 sec or greater developed in precordial leads to the right of the zone of transition In all cases Q waves were present in Leads V_1 and V_2 and frequently extended to include V_3 and V_4

During 2 years (1969 and 1970) most patients with anteroseptal infarction and acute RBBB with or without partial bilateral BBB were treated in the coronary care unit by passing a bipolar electrode catheter under fluoroscopic control from an arm vein to the apex of the right ventricle the catheter being attached to a ventricular triggered demand pacemaker In some patients in whom the QRS voltage was insufficient to trigger this pacemaker a fixed rate pacemaker was substituted and was kept turned off until A V block or asystole developed Patients not treated with prophylactic demand pacing during this time included those in whom there was technical difficulty in positioning the catheter and those patients in whom RBBB had been present for more than one day the danger of A V block being considered not great enough to warrant insertion of a pacemaker Altogether 19 patients had prophylactic insertion of a pacemaker during this period (not all were paced) and 10 did not During 1967 to 1968 there were 30 patients with acute RBBB complicating anteroseptal infarction in none of whom was prophylactic pacing used Thus over the entire period of this study a total of 40 patients with RBBB and anteroseptal infarction did not have prophylactic pacing

During the whole period (1967 to 1970) fixed rate pacing was used routinely in patients with anteroseptal infarction and A V block which had not been anticipated by prophylactic pacemaker insertion for RBBB Eighteen patients were paced for A V block and 6 were not paced usually because A V block was a terminal event When a pacemaking catheter was inserted it was left in situ for about one week after A V conduction had returned to normal

Results

Natural history of bundle branch block and A V block During the 4 years from March 1967 to March 1971 1 140 cases of acute myocardial infarction were admitted to the coronary care unit the hospital mortality rate for the entire group being 20 per cent Seventy (6 per cent) of these patients had anteroseptal infarction which was complicated by RBBB A V block or both of these lesions Of these 70 patients 51 (73 per cent) died in the hospital (Table I) Of the 19 hospital survivors a further 5 (26 per cent) died during a mean 2½ year follow up period for the survivors Seven patients with RBBB were excluded from the study because the infarct was posterior (4 patients) subendocardial (one patient) indeterminate (one patient) or occurred only during nodal rhythm (one patient)

The association of RBBB (with or without additional ECG evidence of partial bilateral BBB) with A V block is shown in Table II RBBB with left anterior hemiblock occurred as often as pure RBBB but RBBB with left posterior hemiblock was less common Surprisingly A V block occurred as frequently following pure RBBB as when there had been additional anterior or posterior hemiblock Of 61 cases of RBBB 20 (33 per cent) also had A V block

Conduction disturbances due to anteroseptal myocardial infarction and their treatment by endocardial pacing

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It is now recognized that a principal determinant of prognosis in atrioventricular (A V) block due to acute myocardial infarction is the site of the infarct causing the conduction disturbance[1,2] In posterior infarction, ischemia or inflammatory response in the region of the A V node and proximal His bundle causes first second, or third degree A V block while the pacemaker in third degree block tends to be stable with normal QRS complexes [3] In anteroseptal infarction on the other hand, extensive septal ischemia leads to right bundle branch block (RBBB)[2,4,5] or partial bilateral bundle branch block[6] and this may go on to unstable complete heart block (CHB) and ventricular asystole[2,5,7] The prognosis in A V block due to posterior infarction is determined mainly by factors unrelated to the conduction disturbance [8] Conduction disturbances due to anterior infarction carry a poor prognosis probably because extensive myocardial necrosis is usually present in these cases[1,2]

The frequency of episodes of ventricular asystole during the course of A V block due to anterior infarction suggests that endocardial pacing might improve prognosis Moreover, the frequency of RBBB or partial bilateral BBB as a forerunner of A V block raises the question of prophylactic demand pacing in acute RBBB due to anteroseptal infarction particularly as A V block often heralded by asystole occurs in up to one third of cases[5,7,9] The purpose of the present paper is to report the results of prophylactic pacemaker insertion for RBBB in 19 cases to compare them with 18 patients treated by pacing after the onset of A V block and to review both series of patients in the light of total experience with conduction disturbances in anteroseptal myocardial infarction over a four year period

Patients and methods

The subjects for our study were acutely ill patients who were admitted to a four bed coronary care unit Those patients over 70 years of age were usually excluded because of the shortage of beds The electrocardiogram (ECG) was continuously monitored with frequent inspection of the QRS duration and 12 lead ECG s were taken twice daily or as soon as QRS widening was seen in the monitoring lead Uncompli

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Table II RBBB in anteroseptal infarction Mortality rate and incidence of A V block and asystole in patients with and without additional ECG evidence of partial LBBB

Conduction disturbance	*No of cases*	*Hospital mortality rate*	*A V block*	*Asystole*
Pure RBBB	28	18 (64%)	9 (32%)	9 (32%)
RBBB with left anterior hemiblock	27	20 (74%)	9 (33%)	6 (22%)
RBBB with left posterior hemiblock	6	5 (83%)	2 (33%)	2 (33%)
Total	61	43 (70%)	20 (33%)	17 (28%)

Table III Pacing in anteroseptal infarction Effect of prophylactic endocardial pacing for acute RBBB on hospital mortality rate

Conduction disturbance	*Prophylactic pacing*		*No prophylactic pacing*	
	No of cases	*Hospital mortality rate*	*No of cases*	*Hospital mortality rate*
RBBB not developing A V block	14	10 (71%)	27	17 (63%)
RBBB later developing A V block	5	4 (80%)	13†	11 (85%)
Total cases of RBBB	19	14 (74%)	40	28 (70%)

*2 patients RBBB w [illegible] resol[illegible] of A V block.
†Pacing was used in 10 of these patients when A V block occurred (see Table IV)

In the present series in which autopsies were done on 70 per cent of patients who died occlusion or gross narrowing in the proximal 4 cm of the left anterior descending artery occurred in all but one case although in approximately one half of the patients severe narrowing of the right and/or circumflex arteries was also present This finding is not unexpected as the proximal part of the right bundle branch in man is supplied by the first septal perforating branch of the anterior descending artery [1 13] and this arises about 4 cm from the origin of the left coronary artery from the aorta [14]

The over all mortality rate of 73 per cent in the present series agrees with that found by Julian and colleagues [6 7] though it is much higher than that reported by Scanlon and associates [9] many of whose patients were not admitted to a coronary care unit As our data and those of Julian and co workers refer to a prospective study of routinely admitted patients it is likely that the higher mortality rate is more correct Our results do differ from those of some other workers in two respects however First in our experience RBBB nearly always complicates anteroseptal infarction and is uncommon in posterior infarction Second we have been unable to correlate the subsequent appearance of CHB/asystole with previous ECG evidence indicating partial LBBB in addition to RBBB [11]

Regarding the first of these differences it would be expected from anatomical evidence[1 14] that RBBB should be commoner in anteroseptal infarction due to proximal occlusion of the left anterior descending artery and it could also be predicted that left anterior hemiblock but not left posterior hemiblock would be caused by such a lesion [12] Such a purely anatomic explanation is unlikely to be more than partly true however since coronary atheroma usually involves all three vessels and the extent of ischemia probably depends as much on coronary dominance and the pre-existing distribution of atheroma as on the final site of arterial obstruction causing the acute infarct Differences of this kind may account for the higher incidence of RBBB in posterior infarction found by some previous

Table I. Incidence and mortality rate of conduction disturbances in anteroseptal infarction

Conduction disturbance	*No. of cases*	*Hospital mortality rate*
RBBB and A-V block*	20	16 (80%)
RBBB without A-V block	41	27 (66%)
A-V block without RBBB	9	8 (89%)
Total	70	51 (73%)

*RBBB was not detected until after resolution of A-V block in two patients.

and this proportion was no different whether hemiblock was present or absent.

Prophylactic pacing for RBBB. In the patients who had prophylactic demand pacing for RBBB (Table III), A-V block subsequently occurred in approximately the expected proportion of 5 out of 19, or 26 per cent, and it occurred within 48 hours of insertion of the pacing catheter in all cases. The onset of A-V block was shown by the occurrence of stable pacing at the natural rate of the pacemaker, and A-V block or asystole when the pacemaker was turned off. Only one of these 5 patients survived to leave hospital, but in his case prophylactic demand pacing was considered to have been lifesaving. This patient's history is briefly summarized in Fig. 1.

Pacing for established A-V block. Of the 18 patients who were paced after the onset of A-V block (Table IV), 8 presented with A-V block, while 10 presented with RBBB which progressed to A-V block and did not have prophylactic pacing (see previous section and Table III). Fourteen (78 per cent) of these patients died in the hospital. Pacing was thought to have been lifesaving in one of the survivors, and to have contributed to survival in the other three. Transient ventricular arrhythmias sometimes occurred during positioning of the pacing catheter, but in no case was the pacemaker considered to be a cause of death.

The clinical course of the 23 individual patients in whom A-V block and asystole were anticipated (5 cases) or treated (18 cases) by pacing is given in Table V. Although 18 (78 per cent) of these patients died in the hospital, life was prolonged beyond the first occurrence of ventricular asystole from 11 hours to 47 days (median 4 days) in 13 (72 per cent) of these 18 patients. Moreover, normal A-V conduction was restored before death in 6 of the 13 and a stable idioventricular pacemaker was restored following asystole in a further 2 patients. Of the 5 hospital survivors all left the hospital with normal A-V conduction, although one had residual RBBB. Thus pacing probably prolonged survival for a short time at least in most patients and the disturbances of A-V conduction and intraventricular conduction were often reversible. Death still occurred, however, from cardiac failure, cardiogenic shock, or irreversible ventricular fibrillation. In two cases perforation of the interventricular septum preceded death, but autopsy in both cases showed that the pacing catheter had not caused the perforation.

Site of coronary occlusion. Autopsies were carried out in 36 (70 per cent) of the patients who died, and in all but one case there was complete occlusion or gross narrowing of the anterior descending coronary artery within 4 cm. of its origin or in two cases marked narrowing of the main left coronary artery. In approximately half the cases the anterior descending artery was the only major vessel occluded or severely narrowed, while in the other half of cases there was also severe narrowing or occlusion of the circumflex and/or right coronary arteries.

Discussion

The syndrome of anteroseptal myocardial infarction complicated by RBBB carries a grave prognosis due to a number of complications, particularly cardiogenic shock and heart failure, and also the development of A-V block and ventricular asystole in one third of cases.[5] The present results show that these disturbances of conduction may be reversible, and that the mortality rate is nearly as high in patients who do not progress beyond RBBB (64 per cent) as in those who develop A-V block and asystole (80 per cent). This high mortality rate is due to massive interventricular septal myocardial damage. A further feature is that the syndrome is nearly always associated with proximal obstruction of the left anterior descending coronary artery.

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Table V Pacing in anteroseptal infarction Summary of individual cases of A V block and asystole

Patient	Age and sex	Reason for pacemaker insertion	Time of death after onset of infarction (days)	Mode of dying	Time of death after first occurrence of asystole (days)	Conduction at time of death or discharge from hospital
H R	61 M	Prophylactic RBBB	6	Rupture IV septum	3	RBBB
S W	65 M	Prophylactic RBBB	1	Shock	11 hr	Asystole
K W	65 F	Prophylactic RBBB	9	Failure	5	CHB
R McS	43 M	Prophylactic RBBB	4	Shock	2½	CHB
H B	48 M	Prophylactic RBBB	Survived			Normal
F N	59 M	CHB + asystole	3	Shock	2½	Asystole
C H	60 M	CHB + asystole	8	Failure + septal rupture	6	RBBB
D H	42 M	CHB + asystole	13	Ventricular fibrillation	12	RBBB
T P	61 M	Asystole	11	Shock	18 hr	Asystole
E W	57 F	CHB	Survived			Normal
E W	59 M	CHB + asystole	Survived			Normal
H B	66 F	CHB + asystole	3	Shock	Nil	Asystole
F H	59 M	CHB + asystole	Survived			Normal
S M	57 M	CHB	Survived			RBBB
G C	63 M	CHB + asystole	6 hr	Shock	Nil	Asystole
R O	55 M	CHB + asystole	4	Failure	4	Asystole
J R	69 M	CHB + asystole	64	Failure	60	Normal
E I	65 M	CHB	1	Shock	Nil	Asystole
W W	65 M	CHB	14	Pulmonary embolus	No asystole	LBBB
J H	61 M	CHB*	52	Failure	47	LBBB
E C	66 M	CHB	9	Shock	3	Asystole
W R	69 M	CHB*	14	Ventricular fibrillation	12	Normal
R W	7? M	CHB	7	Failure	No asystole	Normal

*Asystole developed after start of pacing

lieve that a good functional recovery is possible in a small proportion of these cases

Although pacing was usually unsuccessful it did help to prolong life for a median period of four days in 13 of 18 patients who died following ventricular asystole complicating A V block Moreover in several of these patients it was shown that both disorders of conduction were reversible Thus pacing could be a useful procedure for prolonging life if some more definitive treatment was available and the predictable occurrence of proximal anterior descending artery obstruction raises the question of surgical treatment of selected patients in the acute phase by bypassing the obstruction with a saphenous vein graft from the aorta [20] The success of this procedure would depend on the degree of reversibility of ischemic changes distal to the arterial obstruction and this is unknown in man Although it has been shown experimentally that complete deprivation of myocardial blood supply leads to irreversible necrosis in one to two hours [21] obstruction to the anterior descending artery does not cause complete cessation of myocardial blood flow which may still be 20 to 30 per cent of the control figure [21] In myocardial infarction in man there is thought to be a considerable volume of tissue which is ischemic but not necrotic and survival of this tissue might be improved by bypassing the arterial obstruction

Summary

Conduction disturbances complicated anteroseptal myocardial infarction in 70 patients admitted to a coronary care unit. The hospital mortality rate of these pa

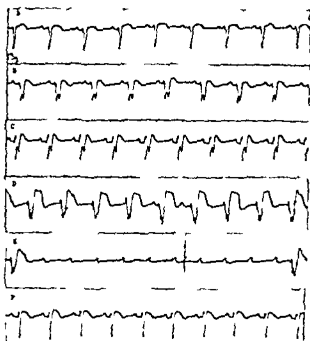


Fig. 1. Monitoring lead from a 48 year old man with acute anteroseptal myocardial infarction (Patient II B of Table V). A, Normal QRS complexes 24 hours after the onset of infarction. B, QRS widening first developed 26 hours after the onset. A 12 lead ECG showed RBBB with mean frontal plane QRS axis of +50 degrees (pure RBBB). C, Following insertion of an electrode catheter attached to a ventricular triggered demand pacemaker 24 hours after the onset, the initial part of the QRS complex is distorted by the pacemaker artifact. D, Thirty hours after the onset, ventricular pacing at 80 per minute occurred intermittently. E, When the pacemaker was switched off at about this time, ventricular asystole occurred. F, Forty eight hours after the onset, QRS duration returned to normal and a 12 lead ECG had reverted to the original pattern of anteroseptal infarction without RBBB.

workers,[6,9] although a recent large series[1] is in agreement with our own findings in this respect.

The lack of correlation between the QRS axis in the ECG and the subsequent development of A-V block confirms our experience with a smaller number of cases[5] and is surprising at first sight. It is known that abnormal right or left axis deviation in the presence of RBBB signifies additional damage to the posterior and anterior division of the left bundle branch,[11] respectively, and it is probable that A-V block in anterior infarction is based on bilateral BBB.[6,16,17] In most patients with myocardial infarction, 12 lead ECG's are not taken more than twice daily, and changes in the QRS axis may not always be apparent in a single moni-

Table IV. Pacing in anteroseptal infarction. Effect of pacing for established A-V block on hospital mortality rate in patients without prophylactic pacemakers

	No. of cases	Hospital mortality rate
Pacing	18	14 (78%)
No pacing	6	6 (100%)

toring lead. In an evolving myocardial infarct, incomplete bilateral bundle branch block might immediately precede A-V block with a duration so short that it would not be detected. Another possibility is that in some cases the LBBB is involved as a whole rather than by its two subdivisions so that a patient would proceed from RBBB to A-V block without any change in axis. Thus the situation is quite different from more chronic forms of heart disease in which gradual progression from partial to complete bilateral BBB occurs.[11,18,19] Although our results do not deny that RBBB with abnormal axis deviation is significant in predicting the onset of A-V block, they do emphasize that in acute anteroseptal myocardial infarction the danger of A-V block and asystole still exists when RBBB occurs with a normal QRS axis.

The use of endocardial pacing both for A-V block, and prophylactically for RBBB has been disappointing in our experience. Although five cases of A-V block with asystole were anticipated by prophylactic pacemaker insertion in RBBB, in only one case was the procedure lifesaving, and of the 18 patients who were paced for established A-V block survival was thought definitely to be due to pacing in only one further case. These results agree with those of Godman and associates,[7,15] who used prophylactic pacing in cases of LBBB as well as RBBB. As a result of this experience it is still our practice to pace all cases of second or third degree block in anterior infarction, but patients with acute RBBB are not now paced routinely as a prophylactic measure. Patients whom we still consider suitable for prophylactic demand pacing are younger patients with absent or slight cardiac failure and shock, as we be-

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

The medical treatment of angina pectoris
V Long acting nitrites as antianginal drugs

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Numerous long acting nitrites have been advocated for the treatment of angina pectoris However their efficacy in the treatment of angina pectoris has not been adequately established[1,2] Long acting nitrites do not appear either to increase the oxygen supply to the myocardium or to decrease the myocardial oxygen demand and therefore are ineffective as antianginal agents[3] The following discussion will cite some of the studies which show that long acting nitrites are ineffective as antianginal agents

Fisch and DeGraff[4] reported that pentaerythritol tetranitrate isosorbide dinitrate and Itramin tosylate studied by blind procedures in uniform as well as in maximally tolerated doses were not statistically superior to placebo in reducing the frequency of anginal attacks

In a double blind study involving 23 patients with angina pectoris due to coronary artery disease Kalmanson and his associates[5] found that pentaerythritol tetranitrate 10 mg 3 times daily and 20 mg 3 times daily compared to placebo had no beneficial effect on the number of anginal attacks or the number of nitroglycerin tablets used The electrocardiographic (ECG) response to the two step exercise test was similar whether the patients were receiving pentaerythritol tetranitrate or placebo in this study Dewar and his associates[6] found in a double blind study involving 19 patients with angina pectoris that pentaerythritol tetranitrate 30 mg 3 times daily or 60 mg 3 times daily compared to placebo did not significantly affect the number of anginal episodes or the number of nitroglycerin tablets consumed

In a double blind study involving 30 patients with angina pectoris due to coronary artery disease Oram and Sowton[7] reported that compared to placebo neither pentaerythritol tetranitrate 30 mg 3 times daily nor propatyl nitrate 30 mg 3 times daily significantly decreased the number of attacks of angina pectoris Dagenais and his associates[8] showed in 15 patients with angina pectoris due to coronary artery disease that compared to placebo pentaerythritol tetranitrate 20 mg or 40 mg did not significantly improve the mean exercise duration or improve ischemic ECG abnormalities

Evans and Hoyle[9] found that only 3 of 21 patients (14 per cent) with angina pectoris had an improvement in the number of

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tients was 73 per cent. Right bundle branch block (RBBB) was the commonest abnormality, and this progressed to complete atrioventricular (A-V) block in one third of cases. Nearly all cases of A-V block were complicated by episodic ventricular asystole. Surprisingly, A-V block was *no more* common in patients showing partial left bundle branch block (LBBB) in addition to RBBB (partial bilateral BBB) than in those who had pure RBBB. In patients who died, proximal obstruction of the anterior descending coronary artery was a constant finding, although extensive involvement of other vessels was also frequent.

Neither prophylactic demand pacing for RBBB *nor pacing for established A-V* block appeared to reduce the high hospital mortality rate, although pacing was considered to have been life saving in two patients. Pacing prolonged life for a few days in a large proportion of patients who died, however, and in several of these patients the conduction disturbances were reversible and death finally occurred from another cause. Pacing would be a useful temporary procedure if some more definitive treatment for this condition was available.

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anginal episodes on 120 mg of mannitol hexanitrate 3 times daily whereas 8 of these 21 patients (38 per cent) had an improvement in the number of anginal attacks on placebo therapy These investigators also found that none of 20 patients with angina pectoris improved on 30 mg of oral erythrol tetranitrate 3 times daily whereas 8 of these 20 patients (40 per cent) had an improvement in anginal episodes on placebo Willis and Duff[10] have also reported that erythrol tetranitrate and mannitol hexanitrate were of limited usefulness in the treatment of angina pectoris

Cole and his associates[11] found that a 15 mg rapidly disintegrating buccal tablet of erythrol tetranitrate (Cardilate) prescribed 4 to 8 times daily for three to six week periods to 9 patients with angina pectoris caused no improvement in anginal attacks in 6 of these 9 patients None of these 9 patients asked that this drug be continued past its scheduled use Friend and his associates[1] showed in a double blind study involving 7 patients with angina pectoris that Triethanolamine trinitrate was not superior to placebo in decreasing the number of anginal episodes

In a double blind study using 24 patients with angina pectoris due to coronary artery disease we[13] found no significant difference in exercise performance whether oral isosorbide dinitrate or oral placebo was given The exercise studies were performed 2 hours after the administration of medication in this study

In a double blind study involving 21 patients with angina pectoris due to coronary artery disease Goldbarg and his associates[14] reported that isosorbide dinitrate prescribed orally 10 mg 4 times daily was no more effective than placebo in reducing the number of anginal episodes or the number of nitroglycerin tablets used Isosorbide dinitrate was also ineffective in improving exercise performance or the ischemic ST segment changes following exercise in this group of patients

We[15,16] found in a double blind study that isosorbide dinitrate administered sublingually 5 mg 4 times daily to 10 patients with angina pectoris due to coronary artery disease was not significantly better than sublingual placebo in reducing the number of anginal episodes requiring nitroglycerin in improving exercise tolerance or in improving the resting or exercise ECG The exercise studies and exercise ECGs in this study were performed 60 minutes after the administration of medication

Using doses of sublingual isosorbide dinitrate and sublingual nitroglycerin matched to produce equal physiologic effects at rest in 8 patients with angina pectoris due to coronary artery disease Goldstein and his associates[17] showed that sublingual isosorbide dinitrate was not significantly better than sublingual nitroglycerin in improving exercise performance or in delaying the onset of ischemic ECG changes during exercise The magnitude and duration of the beneficial effects on exercise capacity caused by sublingual isosorbide dinitrate and sublingual nitroglycerin were indistinguishable in this study Since sublingual isosorbide dinitrate is ineffective as a long acting nitrite[6,1] not more effective than nitroglycerin as a short acting nitrite[17] and more expensive than nitroglycerin there is no justification for prescribing isosorbide dinitrate

Finally my attitude toward long acting nitrites may be summarized by quoting Modell[18] as follows 'The lack of faith of the pharmaceutical industry in its long acting nitrites is nicely demonstrated by the rash of these agents that are now being put up in special delayed action forms What is even more delayed is the proof that the have any merit whatever '[18]

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Determination of hemoglobin oxygen content from per cent saturation data by nomogram

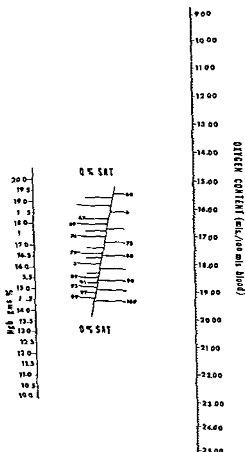


Fig 1 Hemoglobin-O_2 saturation-O_2 content nomogram

In the process of determining cardiac output utilizing the classic Fick formula O_2 content derivation is necessary In our laboratory as in others the longer Van Slyke procedure has been rapidly replaced by oximeter determination of per cent saturation of blood This latter determination requires conversion of the per cent saturation to O_2 content prior to its utilization in the Fick formula The conversion process i based on the assumption that 1 Gm. of hemoglobin combines with 1 34 ml of O_2. The 100 per cent O_2 capacity is calculated for the patient s hemoglobin and the O_2 content for the actual per cent saturation is calculated proportionately

While these calculations are not difficult it seemed obvious that the relationship of the hemoglobin per cent saturation and O_2 content could be expressed in a nomogram. A survey of the English literature and the various commercial sources fails to reveal such a nomogram thus we derived and produced the nomogram presented in Fig 1 Provision wa made for a wide range of hemoglobin levels with inclusion of the polycythemic range The lower limit of 10 Gm per cent of hemo lobin on a nomogram represents the lowest level acceptable to us in patients undergoing elective study

It is our intent simply to make a tool which has been useful in our hands available to those who may see fit to use it.

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Annotations

Effects of antianginal medication on hemoglobin affinity for oxygen

Angina pectoris is the result of myocardial ischemia induced by coronary insufficiency which is caused by disproportion between oxygen supply to the myocardium and myocardial demand for it Theoretically it can be relieved by either an increase in coronary blood flow a reduction of myocardial oxygen requirement or an improvement of oxygen diffusion from blood to myocardial tissue In spite of extensive studies concerning the effects of antianginal medications on the first two mechanisms the third circumstance has never been investigated Therefore we designed an in vitro study on the effect upon hemoglobin affinity for oxygen of nitroglycerin which is known as the most effective in the relief of angina pectoris

Human hemoglobin solution buffered to 0 1M phosphate buffers at various pH values was prepared in a cuvette in a dose of approximately 0 05 μmole Nitroglycerin was added to the solution in an amount of equivalent mole The cuvette was evacuated to obtain completely deoxygenated hemoglobin Absorption spectrum was measured with a Hitachi automatic recording spectrophotometer at *500 to 650 mμ Then a known amount of air* was introduced into the cuvette repeatedly Spectrophotometric measurements were repeated after each admission of air until completely oxygenated hemoglobin was obtained The percentage of oxyhemoglobin was calculated at each added increment of partial pressure of oxygen[1] and plotted on a graph Hill s constant n was obtained from the slope of the plot of log $Y/1-Y$ against log Po_2 where Y is the fraction of oxyhemoglobin and Po_2 is the partial pressure of oxygen

The oxygen equilibria measured at different pH are summarized in Fig 1 in which P_{50} oxygen pressure at half saturation *is plotted against pH* As shown in Fig 1 the value of P_{50} increased as the pH was decreased indicating Bohr s effect However there was no significant difference in their relation ship between control (open circles) and nitroglycerin (closed circles) group Also there was no change in n value after nitroglycerin administration

A decreased affinity for oxygen of hemoglobin has been demonstrated in blood from patients with high altitude exposure[2] chronic anemia[3] arterial hypoxemia due to either congenital heart disease chronic pulmonary disease[4] or low output heart failure[5] While such a reduced affinity of hemoglobin for oxygen has been considered to be a compensatory adjustment to tissue hypoxia Eliot and Bratt[6] postulated that an abnormal hemoglobin could contribute to the paradox of myocardial ischemi observed in patients without demonstrable coronar disease Later this postulation was found not to b applicable in the patient studied by Whiting an associates[7] The assumption that the prompt reli of angina pectoris by nitroglycerin might be at tributed to the transiently augmented relea e o oxygen from blood to myocardial ti ue was nc proved in the present study However con iderin the changes in hemoglobin affinity for oxygen a varied conditions mentioned above further studie investigating the role of such a mechani m in th relief of angina pectoris would still seem valuable

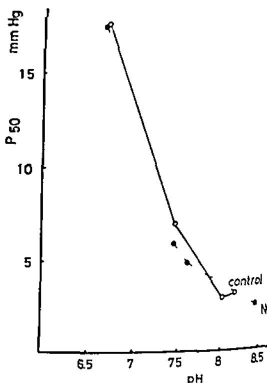


Fig 1 The effect of nitroglycerin on the relationsh between P_{50} and pH

We wish to acknowledge the helpful advice c Drs Jugoro Takeuchi and Yoshiki Sugita

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his representative in constant attendance. However the physician too often takes his nurse for granted assuming her to be a person with clairvoyance a person who needs no consideration in planning therapy for she has feminine intuitive powers and knows what the doctor is thinking In fact, she has been trained specifically for this patient during the particular illness with all of its manifestations and potential complications She is merely told The orders are written I ll be back shortly Perfect care by the nurse is then expected by the busy physician Good results can occur only in spite of this practice

The physician should study the patient carefully After the study is completed the physician should meet with his nurse review the patient s illness and diagnosis objectives in therapy complications and their manifestations to be anticipated and the therapeutic orders. The details of and reasons for objectives in management should be discussed with the nurse The importance of rest sleep procedures and drugs limitations of visitors avoidances of needless and disturbing talking to the patient, frictions in conversation and tone of voice and the like should be stressed The need for sympathy but not annoyance by overindulgence should be emphasized The nurse should be made to realize that she is an indispensable member of the team and that constant dedicated effort is expected of her This type of discussion should apply to all nurses on duty The discussions with each nurse not only permit the physician to decide if the nurses are adequate and compatible with the personality and illness of his patient but at the same time they make the nurses realize that the physician is serious that his patient s welfare comes first and that he will not tolerate carelessness The physician must also modify hospital routine practices as indicated including diet and family behavior all directed to the best interest of his patient.

No nurse should be taken for granted as being capable and as having interest and ability equal to that of the physician all nurses require special instructions and detailed advice from the physician for the management of each patient even if the patient has just been readmitted to hospital Train the trained nurse to fit the need of each patient!

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The three divisions of the interventricular septum of the heart: A classification of septal defects by Manion

As Chief of the Cardiovascular Branch of the Armed Forces Institute of Pathology for nearly two decades the late William C Manion M D examined more than 6 000 hearts with congenital defects A large number of these hearts (more than 1 500), had interventricular septal defects It soon became evident to Dr Manion that the accepted classification of interventricular septal defects into supracristal infracristal was not practical

Because cardiovascular surgeons are accustomed to looking at the hearts of living patients as they are placed on the operating table it has become customary to designate the ventricular septal defects as either supracristal or infracristal Dr Manion a pathologist examined the heart in the vertical position corresponding to its normal anatomic relation to other organs and it became obvious to him that the most appropriate anatomic *division of the septum was the arbitrary separation* of the interventricular septum into three divisions as illustrated in Fig 1 These three divisions are anterior (A) mid septal (M) and posterior (P)

The anterior division (A) includes the right ventricular outflow tract and is anterior to the crista supraventricularis (CS) and conal papillary muscle group (CM) The cardiovascular surgeon often refers to the anterior division as supracristal

The mid septal division (M) is where the most common types of septal defects are found usually referred to as the tetralogy type membranomuscular membranous or muscular septal defects (MS = membranous septum)

In the posterior division (P) the defects always involve the muscle Defects in the posterior division are not common comprising only about 5 per cent of the 1 500 interventricular septal defects on file in the Manion Laboratory of Cardiovascular Pathology

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*The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense

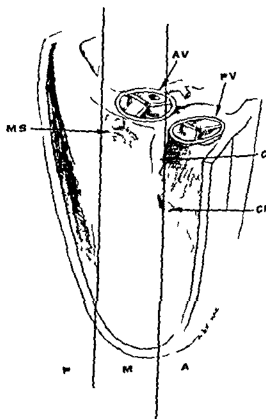


Fig 1 Diagrammatic representation of the three divisions of the interventricular septum proposed by Manion *AV* aortic valve *PV* pulmonary valve *CS* crista supraventricularis *CM* conal papillary muscle *MS* membranous septum *A* anterior division of septum *M* midseptal division *P* posterior division of septum

The nurse and the heart patient

The impeccable care of the sick requires more than the physician s medical knowledge and good bedside manner This is best exemplified by the heart patient Patients seriously ill with heart disease require well integrated care by the entire team of attendants This team is larger than usually realized each member having important responsibilities The physician is the captain of the team and the nurse

is his repre entative in constant attendance How ever the phy cian too often takes his nurse for granted assuming her to be a person with clair voyance a person who needs no consideration in planning therapy for she has feminine intuitive powers and knows what the doctor is thinking In fact, she has been trained specifically for this patient during the particular illness with all of its manifestations and potential compl cations She is merely told The orders are written I ll be back shortly Perfect care by the nurse is then expected by the bu y phy ician Good results can occur only in spite of this practice

The physician should study the patient carefully After the study is completed the physician should meet with h s nurse review the patient s illness and d agnos s objectives in therapy complications and their man fe tation to be anticipated and the therapeutic orders The deta ls of and reasons for objectives in management should be discussed with the nurse The importance of rest sleep procedures and drugs l mitations of vi itors avoidances of needle and disturbing talking to the patient frictions in conversation and tone of voice and the like should be stressed The need for sympathy but not annoyance by overindulgence should be empha ized The nurse should be made to realize that she is an indispensable member of the team and that constant dedicated effort is expected of her This type of discussion should apply to all nurses on duty The di cussions with each nurse not only permit the physician to decide if the nurses are adequate and compatible with the personality and illness of his patient but at the same time they make the nurses realize that the physician is serious that his patient s welfare comes first and that he will not tolerate carelessness The physician must also modify hospital routine practices as indicated including diet and family behavior all directed to the best interest of hi patient

No nurse should be taken for granted as being capable and as having interest and ability equal to that of the physician all nurses require special instructions and detailed advice from the physician for the management of each patient even if the patient has just been readmitted to hospital Train the trained nurse to fit the need of each patient!

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Letters to the Editors

Electrical alternans

To the Editor

Usher and Popp's excellent study, "Electrical alternans" (Am Heart J 83:459, 1972) clearly demonstrates 2:1 pendular rotation of the heart during cardiac tamponade. Their work nicely confirms Feigenbaum and associates[1] in establishing the contribution of this phenomenon to the alternating vector and I am delighted to revise the conclusion from my data (which preceded echocardiography) that alternating intramyocardial conduction was more likely to be the *primary* factor.[2] Despite the excellence of both the presentation and the analysis of Usher and Popp's data, however, several important questions remain based on published observations not included in their own analysis and also on their own explanation of the importance of the volume of effusion fluid in establishing the length of the heart's pendular arc.

The authors state that "electrical alternans only occurs with large pericardial effusions." Clearly this is not the case as demonstrated by the report of a patient with alternation in whom roentgenography demonstrated no visible residual fluid after apparently quantitative removal of effusion (200 ml.) by means of a fortunately placed intrapericardial catheter.[3] Moreover, this patient was shown to have an extraordinarily small pericardial capacity. There was a thick, rigid parietal pericardium which is a usual (possibly invariable) condition for electric alternation.[4] Clearly, these observations impair the authors' conclusion that the "volume and configuration of the pericardial sac define the length of the arc along which the heart moves." Pericardial configuration may indeed have some (speculative) contribution. Yet it is difficult to see how the heart's potential pendular rotation has any more freedom from restraint by any volume of fluid in excess of the minimum needed to distend the pericardial sac.

Interpretations of pressure-volume relationships in tamponade related electric alternation and the influence of intramyocardial factors are further complicated by at least four more observations:

1. Decrease and disappearance of alternans following the removal of tiny aliquots of pericardial fluid (e.g., 50 ml. out of over 1,200 ml. without change in heart rate[2]) leaving the heart less compressed but just as free of restraint.[2,4]
2. The occurrence of strict 2:1 alternation despite atrial fibrillation with varying length diastoles.[2]
3. The common occurrence of very large viscous effusions with no evidence of electric alternation.
4. The occasional simultaneous occurrence of electric and mechanical alternans.[4]

Finally, I have personally observed a patient with 2:1 electric alternation during cardiac tamponade who had extensive anterolateral pericardial adhesions.

These comments are intended to emphasize un- answered questions. Drs. Usher and Popp are to be congratulated for an excellent study which is a valuable contribution to the analysis of this fascinating phenomenon.

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Reply

To the Editor

We appreciate Dr. Spodick's comments in light of his long term interest in electrical alternation during pericardial tamponade. While our recent article does not answer all questions arising from cases with this syndrome, the consistent echographic finding of the described oscillation in all cases studied provides obvious evidence for the positional theory of electrical alternans. In addition, the explanation we have proposed is consistent with several of the points raised by Dr. Spodick. The pendular-arc length of cardiac motion should be related to the size or volume of the pericardial sac since it is the wall of this chamber which prevents the heart from continuing along its path. If the volume is small the heart will encounter the far wall of the chamber and will return to a given position with each cycle. However, if the size of the chamber is sufficiently large the time consumed in traversing the whole chamber will be greater than one cycle length and the heart will still be moving along its path when the subsequent electrical activation occurs. In such a condition a critical volume will be reached such that "the removal of aliquots of pericardial fluid" will fail to permit the proposed cardiac motion as the reduced volume itself will provide a restraint.

Viscous effusions may occur without the proper

heart rate pericardial chamber size or shape to provide the conditions we propose to be necessary in most cases of electrical alternans. The case Dr Spodick cites from his 1968 article showed electrical alternans with a small pericardial volume It is intriguing to note that this case also showed adhesions around the great vessels in the basal portions of the pericardium which would shorten the radius of the pendulum and therefore probably decrease the volume needed to provide the motion we associate with electrical alternans

Fig 3 of the quoted 1967 article shows the cardiogram of a patient with atrial fibrillation but we would not agree that it demonstrates strict 2 1 alternation Obviously there are unanswered questions in pericardial tamponade and we hope that this discussion stimulates continued investigations into these problems The use of cardiac echography in such cases should help confirm or deny our hypotheses The demonstration of electrical alternans in the absence of the oscillatory motion displayed in our article would certainly make us revise our conclusions We will look forward to continued personal discussions with Dr Spodick in order to draw on his vast experience in this topic

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The etiology of arteriosclerosis

To the Editor

The annotation The etiology of arteriosclerosis—a thought which appeared in the March 1972 issue of the AMERICAN HEART JOURNAL (83 434 1972) is a refreshingly new approach for the clarification of the arteriosclerotic process Dr Burch daringly brings back to focus the possibility of a more fundamental pathogenetic process of endothelial cell injury and death as an initial step in atherogenesis and subsequent deposition of lipids and calcium In view of recent knowledge of cell membranes[1,2] and the active transport of electrolytes and water requiring expenditure of energy in the form of ATP Dr Burch does not have to struggle to look for a virus particle under each atherosclerotic patch

The mere interference with optimum supply and utilization of the ATP and ATPase enzyme system of the membranes will interfere with the sodium potassium pump thus allowing sodium and calcium to accumulate intracellularly water to passively follow and potassium to leak out—thus causing swelling of the cells If the process reaches a point of no return cell injury will terminate in cell death thus providing the nidus for the deposition of lipids and calcium Most if not all of the factors associated with coronary disease can interfere through different metabolic ways with the sodium and potassium pump causing cell swelling Also a derangement of intra and extracellular ionic balance can explain better the absolute increase of coronary disease in the younger age group in highly competitive societies through stress and endocrine hypersecretion The patchy nature and the erratic patterns of arteriosclerotic plaques suggest that all these contributing factors (including possibly virus infections) at one time or several of the factors at different times cause the initial damage through one common final pathway—interference with the sodium potassium pump cell swelling and eventual death

This concept of pathogenesis of the disease is not new Leaf[3] in an editorial in the American Journal of Medicine suggests cell swelling and death as the initial process in vessel disease However up to now more superficial and dramatic approaches to the over all coronary problem have unfortunately been given priority (venous bypass graft artificial pumps heart transplantation etc) and have captured the imagination of the researchers and diverted vital research money to very questionable solutions Hopefully with the present available knowledge research will be directed toward cell swelling and death as an initial triggering mechanism If the above pathogenetic concept is verified coronary atherosclerosis may become a preventable disease

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Fascicular blocks vs left ventricular hypertrophy

To the Editor

When is a cat not a cat? The answer to this is whenever a cat is a lion or a tiger or any other member of the cat family other than the common house cat. Dr Ray Pryor in his very excellent editorial entitled Fascicular blocks and the bilateral bundle branch block syndrome which appeared in the April issue of the AMERICAN HEART JOURNAL (83 441 1972) has an example of what he calls anterior fascicular block in Fig 1 To my eye this is a classical electrocardiographic example of left ventricular hypertrophy in a 30-year-old man with aortic regurgitation

It is now becoming very popular to call every electrocardiographic phenomenon that has a left axis deviation either left anterior fascicular block left anterior hemiblock or the like We can therefore rephrase my original question about the cats by asking When is a left anterior fascicular block not

a left anterior fascicular block? The answer to this is whenever one has a left axis deviation that can reasonably be expected to occur without invoking the presence of any kind of block in the conducting tissues. Obviously in hypertrophy of the left ventricle the nature of ventricular depolarization will be such that the vectorial forces will be deviated superiorly and posteriorly and to the left. Similarly, for an inferior wall myocardial infarction with the development of marked negativity in the inferior leads one can expect the development of vectorial forces of the frontal plane superiorly and to the left. Although I am certain that left anterior fascicular blocks *might* occur under these circumstances one cannot infer that they *always* occur in these conditions. These conditions in and by themselves will result in a left axis deviation that at times will become quite pronounced.

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Reply

To the Editor:

In reply to Dr. Breall's thoughtful letter, may I point out that most clinical and electrocardiographic pathologic correlative studies have revealed that left ventricular hypertrophy (LVH) *alone* does not cause the frontal plane mean QRS axis to shift into left axis deviation (LAD) territory—i.e., 270 to 330 degrees, the usual range, or 270 to 300 degrees (−60 degrees) using more conservative criteria. *Reference for these studies may be found in our* article on left axis deviation in the September, 1966 issue of the AMERICAN HEART JOURNAL (72: 391, 1966) and more recent references will be found in the editorial under discussion. Patients with LVH and LAD so commonly have fibrosis in the left ventricle at autopsy that anterior fascicular block (AFB) should usually be read on the electrocardiogram (ECG). Patients with LVH but without AFB will have a frontal plane ÂQRS between 345 and 30 degrees or it may be even more inferiorly directed in children and young people with LVH alone. Inferior infarction alone may cause LAD but it can be recognized on the scalar ECG and confirmed by a vectorcardiogram (VCG). With only inferior infarction the ECG shows a QS deflection in Leads III and aV_F and often a Q wave followed by a small r wave in Lead II. *There will be no terminal r wave* in aV_R and the VCG will reveal a *clockwise* loop in the frontal plane. If a patient has inferior infarction *and* AFB the ECG will usually show a QS deflection with a *notch* on the downstroke in Leads II, III, and aV_F, no terminal r in Lead II, but with a small terminal r in aV_R and occasionally a small terminal s wave in Lead I. The VCG reveals a counterclockwise *loop* in the frontal plane with the leftward superior efferent limb due to the inferior infarction and the leftward more superior afferent limb due to the AFB.

Finally, one must watch for pseudo-LAD or axis illusion not uncommonly seen *with emphysema* and this is not due to AFB. Actually, over the years I have become conservative about reading AFB when LAD is associated with low voltage with or without the pseudo-LAD syndrome. Hyperkalemia may cause temporary and reversible AFB if the serum potassium is returned to normal.

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Influence of conductivity of intraventricular mass on QRS amplitude in different vertebrates

To the Editor:

In some articles published by our laboratory we deal with the influence of the conductivity of the intraventricular mass or tissue *surrounding* the heart on the QRS amplitude in different vertebrates. In order to avoid misunderstanding[1] we here clarify some points with more detailed explanation.

*The changes in QRS amplitude caused by bleed*ing or heart overfilling were described as early as 1910.[2] They were related to the high conductivity of the blood as far back as 1923,[3] when an attempt had been made *to prove this theory*, filling the turtle heart either with high conducting blood or with low conducting 5 per cent isotonic glucose solution. Belechradek[3] intended to demonstrate that high *conductive solution* within the heart causes local short circuits which reduce the peripheral *electrical* field and the amplitude of the ECG, while low conductive solution reduces these short circuits, thereby causing augmentation of the QRS amplitude. Closer inspection of the results shows that the increased QRS amplitude (recorded 5 minutes after the administration of the glucose) is due to damage caused *by outflow of the ions from the tissue into the glucose* solution.

Records taken immediately at the start of heart filling with glucose show that the amplitude of the QRS complex in the turtle is decreased, as is the case when saline, olive oil, or air[4] are *introduced*.

These results show that filling of the turtle heart with any kind of conducting material causes changes in the QRS amplitude in the *same* direction.

Moreover, mechanical stretching of the turtle heart (Fig. 1) produces decrease of the QRS amplitude without any filling material. The question therefore is not, as suggested by Pipberger and colleagues,[1] whether there is a linear influence. If the diminishing of the QRS amplitude is related to the short circuits caused by the presence of a good conductor, a lower conducting or even isolating material within the heart cannot possibly have the same type of *influence*. *This is even more markedly* emphasized if air infusion caused a greater decreased of QRS amplitude than Ringer solution.[4]

Wilson and associates[5] dealing with the problem of decreased magnitude of the ECG potential in

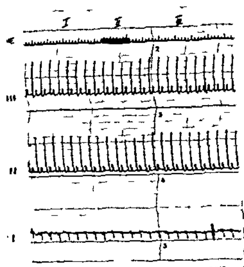


Fig 1 ECG recording (Leads I II and III) from turtle before (I) during (II) and after (III) mechanical stretching of the heart in vivo Time in second

patients with edema pericardial effusion etc. postulated that an increase in the conductivity of the body tissues as a whole or an increase in the conductivity of the tissues lying near the heart will decrease the magnitude of potential differences of the body surfaces [3] The same concept was used by Eyster and colleagues for results obtained in turtles

Our results show that filling of the pericardial sac of the cat either with isotonic saline solution or with olive oil decreases the QRS amplitude independent of the conductivity of these substances In addition we examined the influence of the fluid per se[4] by filling the open pericardial sac with oil or saline The results show that during filling of the open pericardial sac with oil no change of the QRS amplitude was observed—the oil per se has no influence on the QRS amplitude The conclusion drawn from these experiments is therefore that the reduction of the QRS amplitude during filling of the intact pericardial sac with saline or oil is mainly due to the concomitant decrease of the heart filling and not to short circuits surrounding the heart.

Some years later Lepeshkin reported decrease in QRS amplitude caused by bleeding in mammal His explanations did not deal with the influence of the conductivity of the blood Brody[10] Nelson and co-workers Horan and colleagues [4] and Angelakos and associates [7] related this phenomenon to the conductivity of the blood as had been postulated earlier for the increased QRS amplitude during bleeding in turtles and frogs They did not compare these two opposite reactions in different vertebrates and did not go into an explanation of such differences which was one of the consequent aims of our work [20]

Dealing with the influence of the conductivity in the mammalian heart Nelson and associates [2] explain that the effect of a highly conducting medium on an adjacent dipole is to enhance the potentials due to radial dipoles to diminish those due to tangential dipoles and to cause an increase or decrease in potential at different field points if the dipole angle is intermediate [21] A similar idea—the initial ventricular potential complexes are successive growth and decay of two perpendicularly oriented electrical dipoles [21]—can be found already in the early work of Eyster and colleague [22] and Krasno and co-workers

In our experiments with chicken a decrease of the QRS amplitude during bleeding was observed The chicken heart has mainly tangentially oriented dipoles similar to those seen in poikilotherms [23] The decrease in QRS amplitude is therefore not in accordance with the Brody theory

Nelson [24] and Angelakos[14] [7] perfused in their experiments the mammalian heart with fluids of different conductivity but they did not compare good conductors (blood or saline) with isolators (oil or air) They were able to establish a linear relationship between the QRS amplitude and the conductivity of the cardiac perfusate without changes in the filling Our studies did not deal with the influence of the conductivity per se but with the influence of the conductivity *during changes in the heart filling* For this reason we studied the changes by overfilling the cat's heart[4] in vivo with either a good conductor (saline) a low conducting fluid (glucose) or an isolating material (oil) Thus in these setups in one type of experiment (using saline) we produced an increase of the heart filling and of the short circuits inside the heart and in another type of experiment (using oil) we increased the heart filling as before but decreased the short circuits The results[4] show that overfilling of the pumping heart increases the QRS complex independent of the conductivity of the liquid used These results are in opposition to the conclusion of Hugenholtz and associates[25] that increasing blood resistance decreases the magnitude of initial vectors of ventricular depolarization Lowering the hematocrit (lowering the resistance) increases these forces [25] Horan and colleagues [4] filled the left ventricle the right ventricle and then both ventricles with CO Unfortunately there is no comparative tracing (from the same experiment) of heart filling either with CO or saline which show whether during filling with saline the opposite results would have been obtained In their experiments changes in heart position (the direction of R maximum) cannot be excluded We are able to show in the same experiment that either saline or oil increases the QRS amplitude without changes in the heart position

Further studies show that overfilling of the mammal in heart causes changes in the QRS amplitude as well as in the rise time (time to peak) without any changes in the QRS duration (Fig 2) Similar changes were observed in turtles during bleeding These changes were observed in cats with sinus rhythm as well as during artificial auricle pacing used to prevent changes in the heart rate If the QRS changes were due to changes of the intraventricular conductivity why would the time to peak change? For all these reasons we cannot accept Pipberger's viewpoint that our findings lend further support to Brody's fundamental concept [1] On the contrary we agree with the second part of his sen

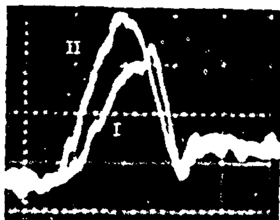


Fig. 2. The superimposed QRS complex of cat electrocardiogram recorded with Tektronix 502 A oscilloscope before (*I*) and during (*II*) overfilling of the heart. Time to peak (Q – R max.) shortened, amplitude of QRS increased.

tence that there are a number of observations which are not as easily reconciled with these concepts.

Dealing with the comparative heart studies, Pipberger *and his co-workers*[1] *state that the differences between mammalian heart and that of the poikilotherm may be explained by the fact that the poikilotherm's thin walled ventricles behave in a fashion similar to the right ventricle of mammals and activation is mainly tangential.*[1] This thin walled possibility based on the Angelakos experi*ments*[17] *has been excluded by us in as yet unpub*lished results. It was also excluded by the results of Horan and colleagues[18] which showed that filling of the right and left ventricle have the same and additive effect on the QRS in the ECG. In our studies[20] we suggest that differences in the conducting system—that is, the presence of a specialized conducting system in mammals and bird, and the absence of such a system in poikilotherms—can explain *the opposite alteration in the QRS amplitude* during bleeding in homoiotherms versus bleeding in poikilotherms. This thought can also explain the results obtained in chickens[24] and was proved in experiments in mammalian heart having at the same time homoiotherm (normal) conduction and poikilotherm-like conduction (bundle branch block).[20]

We agree with Ishikawa and co-workers[25] that "the conclusions from these studies (based on the Brody effect) do not explain the data obtained on the patients in our study whose ECG voltages decreased with increasing heart size. The theoretical studies predict just the opposite. Therefore one must assume that other factors are involved in the ECG changes which occur in congestive heart failure."[25] From our results in healthy mammals and Ishikawa's results[25] in heart failure, we rather conclude that the conductivity or the volume of the conducting fluid inside or outside the heart is not the main cause of the alteration in QRS amplitude.

At the same time we have to emphasize that overfilling of the healthy heart is not the same phenomenon as increased heart size during congestive heart failure. As has been shown[18] during digoxin administration the QRS amplitude increases with the increase in the time to peak (Q-R interval) and the decrease in heart size, while in heart filling increased amplitude *occurs with a decrease in the* time to peak and an increase in heart size.

The influence of digoxin on the QRS amplitude can be observed during tachycardia[?, ?] and during fixed heart rate caused by artificial auricle pacing, and therefore cannot be related to the changes in heart filling as studied by Pipberger and associates.[1]

Increased amplitude of the QRS in cats can be observed even during administration of other drugs and during some physiological conditions now studied in our laboratory.

In conclusion, Pipberger and colleagues[1] wrote in their reply that "*Differences in interpretation provide new stimuli for reevaluation and possibly for* the extension of experimental work."[1] The main purpose of our reports[4, 8] was the same—to give a *new and possibly more correct interpretation* of the well known facts.

Pipberger and co-workers[1] wrote in the same issue that "the observed phenomena are usually interpreted in the light of the Brody effect, which indicates that the presence of a low resistivity mass *(blood) inside the heart chambers tend to increase* electromotive forces in radial direction and to decrease tangential ones. . . . A decrease in the intracavitary *blood* mass caused by acute *bleeding* led, as expected, to a decrease of left ventricular QRS potentials but to an *opposite* effect over the right ventricle where activation is predominantly tangential. . . . *If their (poikilotherms) thin walled* ventricles behave in a fashion similar to the right ventricle of mammals and activation is mainly tangential, the seemingly contradictory findings in homoiotherms and poikilotherms could still be explained on the basis of the Brody effect."[1]

Our results show that the alterations of QRS amplitude in a healthy heart during bleeding are mainly due to changes in the heart filling and the explanation of the opposite reaction of the QRS amplitude in poikilotherms versus homoiotherms is based not on the thin walled ventricle versus heavy ones but on the presence or absence of a *specialized conducting system in the heart.*

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Reply

To the Editor

Since the first Letter to the Editor of Mr Manoach and his co-workers[1] (Am Heart J 83.297 1972) was only marginally related to our report on ECG changes due to cardiac enlargement[2] (Am Heart J 81 635 1971) we made an attempt in our reply[3] (Am Heart J 83 295 1972) to reconcile some of their experimental findings with prevailing concepts on the influence of the intracavitary blood mass on ECG potentials. We felt that in some instances this was possible and in some others it was clearly not. In our original report[2] we had pointed out that none of the mechanisms discussed in this context by others appeared to lead to a satisfactory explanation of the phenomena observed by us and other investigators (references 5 to 7 of our report) Additional data in support of the validity of our results were kindly provided to us by Dr E Harvey Estes Jr As reported earlier he found in 100 young healthy Marine Corps recruits at the end of their basic training a significant increase in heart size accompanied by a significant decrease in QRS potentials It appears to us rather unlikely that these observations can be attributed to cardiac failure These uniform findings led us to the conclusion that *in man* enlargement of the heart leads to diminution of QRS potential and we pointed out the clinical implications of these observations

The ensuing discussion[1,2] dealt primarily with the results obtained by Manoach and co-workers and those obtained by other investigators Some of the findings and their interpretations are clearly contradictory and can be reconciled only by further experimentation This should not be surprising when one considers the great variety of experimental methods used and the inherent differences between species which ranged from lizards and turtles to cats and dogs Since our own experience is limited to observations *in man* we are at least at this time unable to contribute any factual material related to Manoach s discussion Evaluation of results reported by others is frequently difficult when the number of experiments the consistency of results and the detail of methods is not known in sufficient depth In our previous reply[3] we referred therefore only to some pertinent references related to the work by Manoach and associates

Since there is only a very remote relationship between the comments of Manoach and co-workers and our original report it would appear preferable to us if this discussion was continued with the investigators who arrived at experimental results and conclusion which are at variance with theirs They would certainly be better qualified than we to contribute further to the discussion

We can only repeat again our final conclusion of the original report that none of the known mechanisms (including those discussed by Manoach and colleagues) provide an adequate explanation for the observation of decreased ECG potentials in patients with cardiac enlargement We feel confident that further experiments performed in sufficient numbers and with adequate controls will eventually shed more light on some of the vexing problems which appear still unresolved at this time

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Randomized controlled trials of coronary artery surgery

To the Editor

Recent writings[1,2] call for adequately designed and controlled trials of coronary revascularization surgery Repeated comparisons are made between the evaluation of drugs minor surgery and major surgery[4] To date this writer has seen no proposal which includes the details of a protocol for a controlled trial Experimental design is often dismissed as trivial with barriers to acceptance mainly attributed to failings of human nature Indeed barriers to scientific evaluation of coronary revascularization surgery do have their roots in human nature as the following comments will demonstrate

The attitude that any randomized study is better than no study at all is dangerously incorrect A poorly designed study which has the appearance of being adequately designed can give false scientific authority to erroneous findings Whereas doubt may have existed before such a study was published erroneous scientific certainty may tend to replace a more correct doubt In addition to being scientifically sound any study must also be exercisable in the real world in other words it must be practical An examination of the types of control and study design for evaluation of drugs and minor surgery shows that such methods when applied to major surgical procedures are often not practical—They cannot be exercised in a free society[5] On the other hand it is not reasonable to refrain from doing any studies because of the inability to design a perfect study Imperfections in study design must be carefully evaluated In addition different types of studies each having its own strong and weak points can be brought to bear on the central question What is the effect of surgical intervention on the course of atherosclerotic heart disease?

Following are some proposed methods of comparing surgical with non surgical treatment of coronary artery disease and comment

Assignment to a surgical or non surgical group by a purely random method With this method of analysis a coin would be flipped or a random number table would be consulted and the patient assigned to either surgical or non surgical treatment Whereas this method appears to be feasible careful analysis shows that it is not[5] The behavior of people cannot be controlled by the flip of a coin If a patient is refused an operation for any reason he may seek it elsewhere especially if he is highly motivated In addition as soon as word got out that a cardiologist or a group of cardiologists were not sending all surgical candidates for operation referral patterns from other doctors would change It is true that barriers to this type of evaluation are rooted in human nature but they are rooted so deeply in human nature that any pretense at maintaining random grouping would soon fall by the wayside As scientific as this technique is in theory it is not practical

A study of patients who voluntarily refuse operation despite surgical recommendation This is a reasonable control group but there are flaws—one of the major flaws is variability in the strength of the referral Surgery can be proposed to a patient in many different ways and it is very likely that ideal surgical candidates will be more vigorously recommended to have the operation than borderline surgical candidates Another major flaw is that patients can remove themselves from the control group in the same way that they place themselves in it—i e voluntarily We do know that there are

considerable number of patients living and well today for whom operation was recommended but who for their own reason declined One of the major question about these patients is are they doing well because they did not have the operation or are they not having the operation because they are doing well?

Using the patient as his own control preoperative versus postoperative evaluation In general this is a poor method of evaluation by itself Numerous uncontrolled factors such as motivation medication smoking habits dietary habit and a plethora of other factors can bias the results and lead to erroneous findings This is not to say that marked changes in objective findings are not definite proved benefits Indeed they are but over a large series of patients with modest improvement many chances for error can arise

Bypass grafts which have closed Fortunately (for evaluation purposes) there is a documented late closure rate of at least 10 per cent These patients do indeed offer a very sound basis of comparison to patient with functioning grafts We might almost term these patients accidental sham operations There are however some flaws in this comparison If the patient does indeed know that his grafts have failed motivational factors will have been hopelessly biased Another flaw is that the same factors which predispose to a poor prognosis for coronary artery disease may predispose for a poor prognosis for the vein grafts—smoking habits dietary habits personality characteristics and the condition of the distal arterial bed

Comparison of different treatment groups by different advocates In this method of comparison on 1 000 or so patients treated by cardiologist and surgeons would be compared to a similar group of patients treated by cardiologist only The key and tricky phrase here is *a similar group of patients* Although method of assessing coronary artery disease have become quite precise in the last decade there are still many factors to be considered and the judgment as to whether one group of patients was similar to another group is a difficult and time-consuming task Furthermore adequate assessment without coronary arteriography is impossible and the indication for coronary arteriography will be quite different for a cardiologist who refer a considerable number of patients for surgery versus the cardiologist who refers only a few or none of his patients for surgery

Thus it is seen that all of these method of comparison have flaws It would seem that all practical evaluation method should be utilized and their limitation carefully analyzed and reduced as far as possible

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Aspirin and pulmonary lesions in endotoxin shock

To the Editor

After years of intensive laboratory and clinical research with a variety of pharmacological agents therapeutic success in septic shock is far from satisfactory Recently progressive pulmonary failure has been recognized as a fatal complication of clinical septic shock[1,2] Studies done on experimental animal support the clinical picture In primates endotoxin causes marked hypotension and a transient pulmonary hypertension[3] Ultrastructural studies have demonstrated marked polymorphonuclear leukocytic accumulation and fragmentation in pulmonary capillaries after endotoxin[4] and live *Escherichia coli*[5] In cats a similar pulmonary hypertension and pulmonary edema has been reported [7] After intravenous administration of endotoxin the cats become hyperpneic and the lungs show gross edema and hemorrhage at autopsy Similar postmortem findings have been described in patients who received transfusions of blood contaminated with coliform bacteria[8]

Recently we reported our observations on the protective role of aspirin against the pulmonary hypertension in cat after intravenous endotoxin[9] Pulmonary edema and hemorrhage after endotoxin were not seen when the cats had received a prior treatment of aspirin (10 mg per kilogram of body weight) No other pharmacological agent has been found to be effective in protecting the lungs from endotoxin induced damage in cats The mechanism of this protection is not clear since at present the cause of endotoxin induced pulmonary damage is not certain There is strong evidence that in cats dogs and rats the formed elements of blood are necessary in addition to plasma [1] Animal experiment have shown an increase in blood kinin levels in response to endotoxin[2,3] and high level of kinin like polypeptides have been demonstrated in the blood of patients with septic shock [4] In vitro studies showed that endotoxin can release kinins from human plasma and leukocytes[5] and serotonin from rabbit platelets[16] Aspirin has been shown to inhibit endotoxin induced kinin production from human plasma[17] and to inhibit prostaglandin release from human platelets [8] Such effects could be involved in the protective role of aspirin against the endotoxin induced pulmonary lesions

In view of the above observations it might be interesting to investigate whether aspirin will protect the lungs of patients with gram negative septicemia It is unlikely that aspirin would reverse established pulmonary damage in septic shock but a further deterioration might be checked In view

of the pre ent lack of effective therapy we wonder if any physicians might think it justified to try aspirin

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Physiology of Blood and Lymph Vessels Parts I & II Ed ted by M Comel and L Laszt Ba el 1971 S Karger AG 147 pages Price $71 75

The Principles and Practice of Medicine. Ed 18 Edited by A. McGehee Harvey M D D Sc Richard J Johns M D Albert H Owens Jr M D and Richard S Ross M D New York 1972 Appleton Century Crofts Inc 1 650 pages

Sweet and Dangerous By John Yudkin M D New York 1972 Peter H Wyden Inc Publisher 208 pages Price $5 95

Announcements

Training program in pathology of congenital heart disease

A two- to eight week training program in the pathology of congenital heart disease is being offered by the Departments of Pediatrics and Pathology of The Johns Hopkins University Physicians currently enrolled in postgraduate training programs as well as those who have completed training are eligible to apply Trainees will have the opportunity to study specimens from a collection of over 700 hearts with congenital malformations and to correlate clinical data with the defects including history phonocardiograms vectorcardiograms and electrocardiograms radiographs angiograms operative notes and autopsy reports The trainees also will be encouraged to attend conferences and rounds in the Departments of Pediatrics Medicine Surgery Radiology and Pathology and to discuss cases at the weekly Pediatric Cardiology Pathology Conference

A per diem allowance is offered to physicians currently enrolled in a residency or fellowship training program For further information please write to Dr Glenn C Rosenquist Department of Pediatrics The Johns Hopkins Hospital 601 North Broadway Baltimore Md 21205

Fifth Cardiovascular Seminar on Hypertension

Project Cardiac Care of the West Florida Academy of Clinical Cardiology and the Pensacola Educational Program present the Fifth Annual Cardiovascular Seminar devoted to the subject Hypertension—essential renal and renal vascular to be held on October 27 28 1972 in Pensacola Florida

Guest faculty include Drs Harriet Dustan and Ray Gifford of the Cleveland Clinic Dr J C Gunnell of Duke University Medical Center and Dr Walter Kirkendall of the Texas Medical Center

Address all inquiries to Dr J W Fleming Project Cardiac Care 1200 W Leonard St Pensacola Fla

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Editorial

The endurance of the pump

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The recent article by Groom[1] on cardiovascular observations of the Tarahumara Indian runners of Mexico emphasizes how little is known of the limits of human capacity for performance and endurance under rigorous conditions. This lack of knowledge, of course, prevails in numerous other important fields: in physiological processes such as pregnancy and lactation, in the ability to adapt to low dietary intakes, to extremes of temperature, pressure, and other unfavorable environmental circumstances, and in the capacity to continue under prolonged mental anxiety. How did our ancestors fare? How do present-day populations in primitive or underdeveloped countries fare, with their usually monotonous diets and frequent seasonal shortages, impure water, exposure to numerous types of bacterial and parasitic infections, and, not least, in their being prey to diverse taboos and superstitions? Generally, reports indicate that people in these contexts fare far better than is usually appreciated.

Most of these situations, however, relate to conditions common to the existence of the underprivileged. The experience of the Tarahumara Indians is of a different type, for it concerns the very high load of service required of the heart for the performance not only of very active daily work, as vouched for by many observers,[[illegible]-4] but also in the pursuit of pleasurable and enjoyable physical activity.

Groom[1] did not dramatize the performance of the Indians, yet *their feats in the kick-ball races are greater than are conveyed by the figures given.* Groom[1] himself and Balke and Snow[4] described races which they organized, but which were deemed to be "short" ("little more than child's play") and hence requiring no *preparation.* The race held by the latter investigators was 64 km. (40 miles) in length and took about 6½ hours, the average speed being 9.8 km. per hour. The race held by Groom[1] extended for 46 km. *(29 miles)* and the average speed was 9.3 km. per hour. The first point to be stressed is that the ground traversed was not flat; the distance was lengthened by the devious pursuit of the balls up and down over rugged terrain at altitudes of 7000 to 8000 ft. above sea level. ... [1] *Groom* calculated that his runners of 55 kg. mean weight had an oxygen consumption of 2.4 liters per minute—i.e., 43.6 ml. *per kilogram* per minute. For long distance races Balke and Snow[4] estimated a figure of about 43 ml. per kilogram per minute. Oxygen intake falls with the increase *in*

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altitude, a value at 7,000 to 8 000 ft would be about 15 per cent higher at sea level[5,7] Hence for the 46 to 64 km races the figure of about 43 ml per kilogram per minute is equatable to 49 to 50 ml per kilogram per minute at the lower altitude

Balke [8] and later Cooper [9] have shown that the greatest distance that can be run in 12 to 15 minutes provides an accurate prediction of maximal oxygen intake (correlation 0 897) This index adjusted for body weight is the most useful single measurement characterizing the functional capacity of the oxygen transport system (cardiovascular and pulmonary systems) [10] Employing this test on six male Indian runners Balke and Snow [4] over a 15 minute period obtained a mean oxygen consumption of 47 4 ml per kilogram per minute, allowing for altitude, the figure at sea level would be 54 5 ml per kilogram per minute

How does this value compare with the performance figures of Caucasians? Cooper and Zechner [11] using this test, investigated the physical fitness of U S Air Force personnel They found that an oxygen consumption of 51 6 ml per kilogram per minute or more ("an excellent level of fitness") which involved running 2 8 km (1 75 miles) or more in 12 minutes, was reached or exceeded by 6 0 per cent of males at 19 years but by none at 29 years This oxygen consumption figure was thus attained by only a very small proportion of fit American males on a flat track for a few minutes Yet as noted above the same figure is attained by the Indians running over rough terrain for hours or even for days

How do the performances of the Indians compare with those of international athletes? The latter, as shown by Saltin and Astrand [12] reach very high maximal oxygen uptakes of 67 to 85 ml per kilogram per minute however, their performances to provide these data measured on ergometer or treadmill could be continued for not longer than a few minutes Balke and Snow[4] and also Groom[1] stressed repeatedly that it is *the endurance* not the *speed*, of the Indian runners, that is exemplary

For the "short" races described (46 and 64 km), energy expenditure would be about 10 to 12 Kcal per minute[4,13]—i e 600 to 720 Kcal per hour or about 14 000 to 17 000 Kcal if carried on for 24 hours

Both groups of workers[4] insisted that ra[ces] over very long distances are common 'The usual distance covered ranges from 150 to 300 km The total time required to complete such a contest is 24 to 48 hours These long races imply an average speed [of] 6 2 km per hour (two thirds of that in the "short" races), which would require a tot[al] energy cost lower than that indicated above Balke and Snow[4] pointed out tha[t]

So far, physiological evaluation of feats [of] strenuous mountaineering or of long d[is]tance skiing or bicycling competitions [—] the most strenuous activities in ma[n] voluntary physical efforts over many ho[urs] of duration—have yielded a limit of 10 0[00] Kcal of energy expenditure within [24] hours These investigators and [also] Groom[1] are certain that the total ener[gy] cost for a 160 km (100 mile) race by [the] Indians would be well beyond 10 0[00] Kcal *per diem*

Other aspects add to the credit of [the] Indians achievement (1) Not ju[st the] physically elite of the Indians are fo[n]d [of] races they are also popular with child[ren and] with women and they often last throu[gh]out the night (2) Virtually an exclu[sive] vegetarian diet is consumed, composed [of] maize beans and vegetables intake [of] animal protein and fat are very low [It is] important to note that good endura[nce] performances were obtained in a societ[y in] which undernutrition and malnutrition [are] reported to be widespread[1] It has [been] demonstrated that capacity for work [is] regulated by muscle glycogen which s[tor]age material is most effectively built up [by] a high carbohydrate diet [14] carbohydr[ate] foods are the primary components of [the] Indians diet (3) Atmospheric temperat[ure] may be high in the race organized by B[alke] and Snow [4] the average temperature [was] 27° C (81° F)

While recognizing the excellence of [the] feats described many may consider t[hat] the bearing of the context of the Ind[ian] runner on the everyday sedentary life [of] western man is so remote as to be wh[olly] irrelevant Two comments may be ma[de] First, the principal lesson to be learne[d is] probably one of human physiology T[he] burden of the experience of the Indian[s is] that in a relatively primitive context th[e] prolonged physical activity involving

x	Rv	R	Front	L sag	Hori	Vector angle	Qr
0	1 7	0 8	CW†	CCW	CCW	40	0 1
7	1 8	2 2	CW	CCW	CCW	330	0
8	0 9	1 2	CW	CCW	CCW	20	0 3
0	1 5	1 0	CW	CCW	CCW	3	0 35
2	0 8	1 1	CCW	CCW	CCW	331	0 1
6	1 0	0 9	CW	CCW	CCW	0	0 3
75	1 8	1 25	CW	CCW	CCW	342	0 29
87	0 63	0 67	CW	CCW	CCW	345	0 26
56	2 89	2 71	CW	CCW	CCW	314	0
85	1 04	1 25	CCW	CCW	CCW	0	0 35
89	1 35	1 00	CW	CCW	CCW	18	0 1
94	0 65	0 65	CW	CCW	CCW	25	0 1
68	1 22	0 80	CW	CCW	CCW	20	0 29
49	0 54	0 55	CW	CCW	CCW	325	0 08
5	0 6	0 4	Fig-of 8 CW	CCW	CCW	324	0 05
42	1 23	1 10				355	0 178
1 5	0 6	0 55				314	0
5	2 89	2 71				40°	0 35

classic rapidly progressive X linked pseudohypertrophic dystrophy of Duchenne limb girdle dystrophy of Erb facioscapulohumeral dystrophy of Landouzy Dejerine and slowly progressive Duchenne's dystrophy or limb girdle dystrophy with pseudohypertrophy Convincing evidence of heart disease has been found in each of these four categories although with varying incidence and severity Cardiac involvement is most prevalent and readily detected in the classic X linked pseudohypertrophic dystrophy of Duchenne and least frequent and most subtle in Erb's limb girdle dystrophy and facioscapulohumeral dystrophy[2] Patients with slowly progressive Duchenne's dystrophy or limb girdle dystrophy with pseudohypertrophy fall somewhere in between

Classic pseudohypertrophic Duchenne's dystrophy is an X linked recessive disease that occurs almost exclusively in male subjects and characteristically begins during the first five years of life[2 14] Initial involvement of the pelvic girdle causes exaggerated lumbar lordosis protuberant abdomen and clumsy waddling gait Pseudohypertrophy of the calves is especially marked There is subsequent spread of the dystrophy to the shoulder girdle Progression is usually constant and often rapid with the development of contractures and skeletal deformities that result in confinement to wheel chair or bed within a decade of onset Although patients generally succumb to inanition and infection (especially pulmonary) terminal heart failure often follows years of stability during which the only suspicion of myocardial involvement is the distinctive ECG[2 3] In addition a variety of rhythm disturbances have been observed including inappropriate or labile sinus tachycardia premature beats (ventricular or supraventricular) atrial flutter paroxysmal ventricular tachycardia and excessive myocardial irritability during cardiac catheterization[2] Necropsy studies have thus far shed little light on the causes of the arrhythmias degeneration of nerve fibers to the sinus or atrioventricular nodes has not been consistently demonstrated[4] but in an occasional patient the arteries to both cardiac nodes have been abnormal[4 1]

Clinical detection of cardiac involvement in classic Duchenne's dystrophy is relatively easy because of the pattern exhibited by the 12 lead scalar ECG[1 2] Tall right precordial R waves with increased R/S

Table III Results in Group II

Patient	Age	PR	QRS	QT	Rate	Q amp	Q durat	QR...
1	16	0 10	0 09	0 33	100	2 2	0 03	2 [illegible]
2	14	0 14	0 07	0 35	83	0 65	0 035	0
3	18	0 14	0 08	0 34	83	1 75	0 05	1 0
4	15	0 08	0 075	0 32	75	1 25	0 04	1 [illegible]
5	15	0 12	0 08	0 30	100	1 26	0 03	1 [illegible]
6	14	0 14	0 08	0 34	94	1 4	0 035	0 [illegible]
7	13	0 16	0 08	0 30	83	0 10	0 015	0 [illegible]
8	17	0 14	0 07	0 31	94	0 28	0 03	0 [illegible]
9	18	0 13	0 09	0 35	94	0 86	0 035	1 [illegible]
10	19	0 13	0 08	0 30	100	1 1	0 035	0 [illegible]
11	14†	0 08	0 08	0 32	105	0 44	0 03	0
11	19†	0 13	0 07	0 31	94	1 2	0 03	1 [illegible]
12	13	0 11	0 07	0 31	115	0 7	0 03	0 [illegible]
13	27	0 20	0 07	0 36	72	0 47	0 208	0
14	25	0 16	0 07	0 34	72	0 35	0 03	2 [illegible]
15	15	0 12	0 08	0 36	105	0 87	0 04	2 [illegible]
16	18	0 11	0 08	0 28	108	0 78	0 03	1 [illegible]
17	17	0 12	0 08	0 30	125	0 59	0 04	8 [illegible]
18	16	0 13	0 08	0 40	90	1 65	0 04	2 [illegible]
19	15	0 12	0 075	0 32	105	0 50	0 055	1 [illegible]
20	17	0 13	0 08	0 32	115	0 78	0 03	[illegible]
Mean						0 91	0 033	1 [illegible]
Range						0 1 2 2	0 015 0 055	0 [illegible] 8 [illegible]

*Studied at age 12
†Studied at age 14 and 19

amplitude ratios and deep limb lead and lateral precordial Q waves form a familiar motif that is related specifically to the classic pseudohypertrophic X linked Duchenne's dystrophy (Fig 1) At times the deep Q waves coexist with altered shapes of right precordial R waves (RSr′ or polyphasic QRS) Affected siblings often exhibit identical tracings The existence of these characteristic electrocardiographic patterns in classic Duchenne's dystrophy is no longer debated but their mechanism is[3,4] Studies thus far have made it clear that the patterns are *not* related to thoracic deformity, thoracic muscle atrophy pulmonary hypertension hypertrophy of right ventricle crista supraventricularis or interventricular septum abnormalities in right ventricular conduction or coexisting coronary arteriopathy[3,4] Two theories are current (1) that the electrocardiographic patterns reflect dystrophic lesions in the myocardium,[3,4] and (2) that the patterns represent a genetically determined persistence of the ECG of infancy or early childhood[1] Postmortem observations in two patients suggested that the anterior shift of the QRS (tall right precordial R waves) was related to loss of posteriorly directed electrical forces caused by ve scarrin

extremely high sustained level of energy expenditure (possibly the highest known) does not extend the heart beyond its capacity Just as the body can respond better than would be expected to adverse environmental circumstances of the type mentioned in our first paragraph so the heart under the conditions described has far greater reserves of capacity than is usually credited The second comment is that the performance of the Indians constitutes an extreme rather than a unique situation The majority of the world s population especially in the East still work hard physically this is so even with the elderly In Africa in studies on series of aged country Bantu people of 90 to 110 years the striking feature observed is their activity in and around their dwellings and their ability still to walk long distances[1] Moreover in Europe in villages in the Alps at altitudes of 4 000 to 8 000 ft one report has related that farming is still performed under extremely difficult conditions Men frequently carry loads of 100 pounds or more loads of up to 60 pounds have been seen to be carried by elderly women[16] In the United States there are doubtless large numbers of young and old people who still work very hard physically Yet habitual activity cannot but progressively decline Kannel[17] has written forcibly that with the proportion of virtually motionless persons in the general population growing the need to regain the habit of walking and climbing stairs seems urgent It is time to consider engineering physical activity back into daily living to counter the sloth and gluttony promulgated by modern technology and changing mores[17] But how can this trend be combatted in a population in which there is now one new car *annually* per 70 persons[18] At present in many western countries heart disease now accounts for about a third of all deaths The fault however lies not with an inherent weakness of the heart as a pump for man s premature death the responsibility lies in the circumstances of sophistication and opulence

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Clinical communications

The vectorcardiogram in Duchenne's progressive muscular dystrophy

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A variety of heredofamilial neuromyopathic disorders are associated with abnormal electrocardiograms (ECG's)[1] but only one—the classic X-linked pseudohypertrophic dystrophy of Duchenne—results in a distinctive uniform electrocardiographic pattern.[2-6] Investigation of this electrophysiologic aberration has both theoretical and practical value, and one cannot help but respond to the challenge posed by the mystery of its cause. A number of publications have been devoted to the ECG itself,[2-8] but relatively scanty attention has been paid to the vectorcardiogram (VCG).[2, 9] Such attention has been limited both in number of observations and in the extent of analysis. Accordingly, a prospective study of the VCG was undertaken in 34 patients with classic, rapidly progressive X-linked Duchenne's dystrophy.

Methods

VCG's were recorded using the Frank system[10] and standard 12 lead scalar ECG's were taken with commercial direct writers.

Patients were selected only after an u[...] equivocal clinical diagnosis of Duchenn[e] muscular dystrophy had been establish[ed] by one or more consulting neurologists [...] the Muscular Dystrophy Clinic of Geor[ge]town University Hospital. The subj[ects] were then divided into two age groups [to] facilitate comparison of their tracings w[ith] vectorcardiographic norms for compara[ble] age ranges. Group I consisted of 15 patien[ts] aged 6 to 12 years (average 9 years). Gro[up] II consisted of 19 patients aged 13 to [...] years (average 17 years). Two patie[nts] were restudied at four to five year int[er]vals, namely, 12 and 16 years and 14 and [...] years. Both of these subjects exhibit[ed] distinct changes in their sequential traci[ngs] so that each of the four tracings will [be] dealt with individually.

Frank lead placements were u[sed] throughout with electrodes attached to [the] fourth intercostal space as recommend[ed] for the supine position.[11] The three orthog[o]nal scalar leads (X, Y, Z) were sim[ul]taneously recorded and frontal, left sag[it]tal, and horizontal loops were in [...]

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x	Ry	Rz	Front	L sag	Hori	Vector angle 16 1	Qv
7	1 9	0 85	CW	CCW	CCW	40	0 4
5	0 5	0 9	CW	CCW	CCW	35	0 23
8	1 2	1 75	CW	CCW	CCW	304	0
0	0 7	1 05	CCW	CCW	CCW	40°	0 4
7?	1 0	1 0	CW	Fig -of 8 predominantly CCW	CCW	?5	0 4
						15°	0 13
) 5	? 0	1 7	CW	CCW	CCW	15	0 13
15	0 03	1 ?	CCW	CCW	Fig of 8 CCW	305	0
83	0 55	1 3	CCW	CCW	CCW	305	0 1
?	0 7	0 48	CCW	CCW	CCW	18	0 ?5
1	1 2	1 5	CW	CCW	CCW	340	0 2
?1	0 65	0 63	CCW	CCW	CCW	330	0 13
	1 25	1 1	CCW	Fig of 8 predominantly CCW	CCW	0	0 65
6	1 6	0 85	CW	CCW	CCW	5	0
7	0 35	0 6	Fig of 8 CCW CW	CCW —	CCW	350°	0 1
1	0 6	0 15	CW	Fig of 8 no predominant pattern	CCW	60	0
14	0 79	0 40	CW	CCW	CCW	73	0 14
72	0 24	0 54	CW	CCW	CCW	7	0 07
19	0 95	0 07	CW	Fig of 8 CCW	CCW	22	0 30
? 06	1 12	0 65	CW	CCW	CCW	50	0 53
) 24	1 00	0 27	Fig of 8 CCW	Fig of 8 CCW	Fig of 8 CCW	108	0 05
) 37	0 22	0 38	Fig -of 8 inverted CCW	CCW	CCW	50°	0 02
0 875	0 88	0 83				17	0 195
0 24	0 03	0 07				304	0-
1 5	2 0	1 75				108	0 65

the posterobasal portion of the left ventricle[4] The abnormally deep Q waves appeared to reflect lateral extension of the scarring[4] The reason for focal localization of the myocardial fibrosis was not determined Striking abnormalities are known to occur in small intramural coronary arteries in Duchenne s dystrophy[13] but the distribution of myocardial scarring has not coincided with the location of the abnormal coronaries[4] In addition distinctive Duchenne ECG s have been found in some female carriers who manifest only enzymatic evidence of systemic myopathic disease[2 4]

The present study used the Frank VCG for the following purposes (1) to add to the scanty body of descriptive information on planar loops and scalar displays of X Y and Z orthogonal leads in classic Duchenne s dystrophy (2) to determine whether or not the Frank VCG serves a useful purpose as a supplement to the standard scalar ECG in such patients and (3) to apply rigid age standards to the analysis of tracings in order to gain insight into the mechanism responsible for the distinctive patterns

Heart rate The rates tended to be rapid (sinus tachycardia) As early as 1904 Meer

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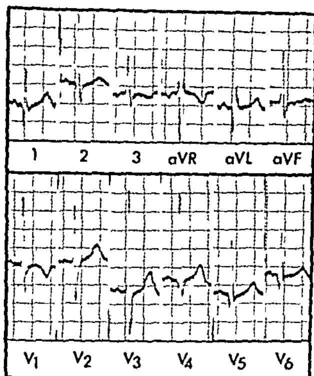


Fig. 1 Scalar ECG in a 14 year old boy with classic Duchenne's muscular dystrophy. There is a tall R wave in Lead V_1 and deep Q waves in Lead I, aVL and V_6.

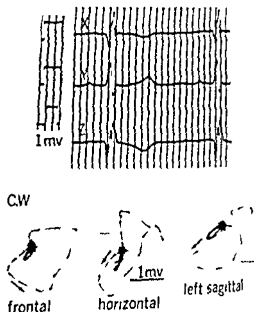


Fig. 2 The scalar and planar Frank VCG in a 19 year old boy with classic Duchenne's muscular dystrophy. The deep Q waves in Lead Z (−1.3 mv) and Lead X (−0.65 mv) are due to the abnormally prominent early rightward and anterior QRS vector forces. The horizontal and left sagittal planar loops show the accentuation of anterior force. Time lines are 0.04 sec apart. Calibration signal is 1 mv. Dots in the loops are 0.004 sec apart.

wein[16] called attention to tachycardia in progressive muscular dystrophy. In 1930 Boas and Lowenberg[17] emphasized that the heart rate was apt to be rapid even during sleep, was frequently labile and was apt to accelerate excessively in response to minimal stimuli. The tachycardia has been considered a manifestation of the "immobilization syndrome," i.e., an exaggerated response to effort or to positional changes in patients confined to wheelchair or bed. The presence of spontaneous tachycardia without apparent provocation makes this explanation doubtful.

P-R interval: Shortened P-R intervals found by others[3,18] were not present in this study or in that reported by Fitch and Ainger[9] when the intervals were corrected for age and heart rate. It is unlikely that delayed atrioventricular conduction is a feature of classic Duchenne's dystrophy.

QRS duration and intraventricular conduction: The VCG's showed no evidence of abnormal intraventricular conduction; the QRS duration was slightly prolonged (0.09 sec.) in only two patients in Group I (age 6 to 12 years). These conclusions confirm previous views that the distinctive morphology of the QRS cannot be ascribed to disordered right ventricular conduction.[24]

The direction of ventricular depolarization: The direction of inscription of the QRS loop was normal in each of the three planes in all patients of both groups. This observation is in accord with that of Fitch and Ainger[9] and is especially important in distinguishing the prominent anterior force in Duchenne's dystrophy from those of right ventricular hypertrophy. In right ventricular hypertrophy the horizontal loop is frequently clockwise, whereas in Duchenne's dystrophy the horizontal loop was never clockwise despite the prominence of anteriorly directed forces.

The QRS pattern: The majority of vectorcardiographic abnormalities (27 of 36) were related to unusually prominent anterior forces (Figs. 2 and 3). In Group I 12 of 15 patients had abnormally large Q waves in Lead Z (the other three showed neither abnormally large Q waves nor abnormally large Q/R amplitude ratios in this lead). In Group II eight of 21 tracings had abnormally deep Q waves in Lead Z and an additional seven tracings showed abnormally large Q/R amplitude ratios in this lead so that 15 of 19 subjects had abnormally prominent ante[illegible] The next

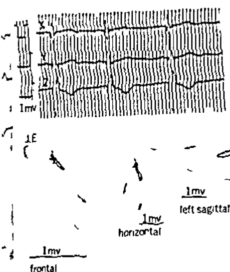


Fig. 3. The scalar and planar Frank VCG in a 16-year-old boy with classic Duchenne muscular dystrophy. The deep Q waves in Lead Z (−2.75 mv) reflect the abnormal early anterior QRS vector forces that are seen in the horizontal and left sagittal planar loops. Time lines are 0.04 sec. apart. Calibration signals 1 mv. Dots in the loops are 0.004 sec. apart.

most frequent abnormality was represented by deep Q waves in Lead X. The abnormally deep Q waves appeared twice in Group I but six times in Group II. There was only one instance in which the deep Q in Lead X was not reflected by abnormally large initial anterior forces in Lead Z. Finally, it is important to call attention to a negative observation, namely, that none of the patients in either Group I or II had abnormally large R waves in Lead X and only two had abnormally tall R waves in Leads Y or Z.

These observations are in harmony with information derived from scalar ECG's which have shown that the distinctive features of the Duchenne tracings are the tall right precordial R waves and the deep Q waves in limb leads (I and aV$_L$) and left precordial leads. It has been proposed that such abnormalities represent a genetically determined persistence of infantile or childhood vectorial and electrocardiographic patterns.[4,5] Let us examine this proposal in the light of currently available information.

The Q/R amplitude ratio in Lead Z reflects the ratio between the anterior and posterior forces in the QRS loop. As a normal child grows and develops, the *posterior* forces progressively increase and the ratio diminishes. In our patients with Duchenne's dystrophy the Q/R ratio *increased* with the passage of time; the average ratio was 1.15 in Group I and 1.64 in the older Group II. This observation implies that as patients with Duchenne's muscular dystrophy age, their vector loops shift anteriorly. This conclusion correlates also with the average half-area vector in Group I which was 355 degrees but in Group II was more anterior at 17 degrees. Two individual patients in Group II further demonstrate the tendency for anterior predominance of forces with aging. One patient at age 12 years had a Q wave amplitude of 1.24 mv. and a Q/R amplitude ratio in Lead Z of 1.24, while at age 16 years the Q wave amplitude was 2.2 mv. and the Q/R amplitude ratio 2.6. A second patient at 14 years of age had a Q wave amplitude of 0.44 mv. and a Q/R ratio of 0.70. At 19 years of age his Q wave amplitude in Lead Z had increased to 1.2 mv. and the Q/R ratio to 1.05.

In infancy and early childhood the greatest incidence of deep limb lead Q waves is in Leads II, III, and aV$_F$;[19] deep Q's in Leads I and aV$_L$ *are exceptional*. In Duchenne's dystrophy prominent Q waves occur in Leads II, III, and aV$_F$, but what is more relevant to the argument is the presence of deep Q waves in Leads I and aV$_L$. *Deep Q waves in Leads I and aV$_L$* cannot be considered persistence of infantile or childhood patterns, and in this study the prevalence of deep Q waves in orthogonal Lead X was greater in older Group II than in younger Group I.

These observations are not consonant with the idea that the distinctive QRS in Duchenne's dystrophy represents persistence of infantile or childhood patterns. What alternative theories can then be proposed? It could be argued that the occurrence of identical ECG's in siblings implies a genetic determinant of the distinctive electrophysiologic patterns. This genetic determinant might result in either focal anatomic lesions in the heart or electrical alterations without detectable anatomic counterparts. A purely electrical explanation is essentially speculative. An anatomic basis for the anterior shift of the QRS and deep Q waves would mean that virtually

identical zones of myocardium were preselected for dystrophic changes by the genetic determinant Despite the fanciful nature of this concept, some evidence suggests that it may be so The prominent anterior forces may represent a relative loss of posterobasal electrical activity as in strictly posterior infarction [2,4,5,6] One autopsy study lends credence to this theory [4] but confirmation awaits further ECG VCC necropsy correlations

Summary

This study represents a Frank system vectorcardiographic analysis of 34 patients with classic rapidly progressive X linked recessive Duchenne s muscular dystrophy The data add to the scanty body of descriptive vectorcardiographic information in this myopathic disorder In addition the VCG was shown to be a useful supplement to the scalar ECG and in the context of this analysis sheds light on the mechanisms responsible for the distinctive uniform electrocardiographic vectorcardiographic patterns in Duchenne s dystrophy The characteristic electrocardiographic changes reside in the QRS conduction abnormalities and rhythm disturbances—except sinus tachycardia—are of incidental importance Previous studies have shown that the distinctive QRS patterns are not due to thoracic deformity, thoracic muscle atrophy, right ventricular hypertension or coexisting coronary arteriopathy The present study confirms that the patterns are not those of right ventricular hypertrophy or abnormal right ventricular conduction and casts serious doubt on the idea that the essential explanation lies in persistence of the electrocardiographic vectorcardiographic pattern of infancy and early childhood The electrophysiologic abnormality may instead represent a genetically determined pattern that stems from disordered electrical activity of a particular zone of left ventricular myocardium

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The infant with transposition of the great arteries

I Cardiac catheterization protocol

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Balloon atrial septostomy (BAS) described by Rashkind and Miller[1] in 1966 provides rapid and effective palliative therapy for the newborn infant with transposition of the great arteries (TGA) The majority of these infants especially those with an intact ventricular septum (IVS) are seriously ill upon arrival in the cardiac catheterization laboratory They may manifest one or more of the following problems (1) congestive heart failure (2) severe hypoxemia (3) metabolic acidosis and (4) hypothermia

In order to insure the best possible chance for the infant s survival it is essential that a certain amount of information be obtained in a minimum amount of time during initial cardiac catheterization (see Table I) Even after successful BAS with an increase in systemic oxygenation hypothermia and metabolic acidosis often necessitate rapid termination of cardiac catheterization An orderly protocol for catheterization that eliminates unnecessary steps and that anticipates any potential difficulties is therefore essential The following procedures and precautions currently followed at the Texas Children s Hospital during initial cardiac catheterization in infants with transposition of the great arteries have been designed with these criteria in mind

Regulation of body temperature

Hypothermia a common and potentially lethal problem in newborn infants with transposition of the great arteries is a special hazard when infants must be transported from another hospital in an outlying area In addition upon arrival at the major hospital or medical center the infant is usually subjected to multiple physical examinations an electrocardiogram (ECG) and chest radiographs all of which may further depress his body temperature unless adequate precautionary measures are taken In order to avoid these problems the use of incubators or radiant heat devices is mandatory to maintain effective body warming prior to the cardiac catheterization Upon arrival in the cardiac catheterization laboratory the infant should be

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Table I. Cardiac catheterization protocol for infants with transposition of the great arteries

A. Establish diagnosis
B. Perform balloon atrial septostomy
C. Obtain essential information
  (1) Pressure data
    a. LA to RA withdrawal pressure both before and after BAS
    b. LV vs. RV pressure
  (2) Associated defects
    a. Patent ductus arteriosus
    b. Ventricular septal defect
    c. Severe pulmonary stenosis
D. Obtain additional useful information
  (1) Pressure and oxygen saturation
    a. All cardiac chambers and great vessels
    b. Before and after BAS
  (2) Pressure gradient in mild to moderate pulmonary stenosis (LV pressure less than 2/3 that in RV)

Abbreviations: BAS = balloon atrial septostomy; RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle.

placed on a radiolucent heating pad and covered with drapes or towels. Rectal temperature should be monitored continuously during catheterization to avoid extreme temperature fluctuations.

Site of cutdown

In infants with TGA, a venous cutdown in the right inguinal region is used for the initial cardiac catheterization. In a newborn infant less than 48 to 72 hours of age, the umbilical vein has been used for both the diagnostic catheterization as well as the BAS.[2] In most instances, however, surgical exposure of the femoral vein is required.

The site of the skin incision for cardiac catheterization in newborn infants differs from that in older infants and children in whom the saphenous bulb lies 0.5 to 1.0 cm. caudal to the inguinal crease; an incision to expose the saphenous vein and bulb will therefore be made at that level. In newborn infants, the saphenous bulb and saphenofemoral junction lie at about the level of the inguinal crease. In these patients Rashkind has recommended that the incision be made 1 cm. cephalad to the inguinal crease at about the level of the inguinal ligament.[3] With this technique, the catheter is inserted into the femoral vein at the level of the inguinal ligament and cephalad to the saphenous bulb. The advantage of this method lies in the fact that the femoral vein at this level is large enough to permit insertion of a No. 6.5 French balloon catheter. There are, however, a number of disadvantages. Ligation of the femoral vein precludes the use of that area for any future catheterization procedures. In addition, if the vein is accidentally torn during attempts at insertion of the balloon catheter, the cephalad portion of the vein will lie at the level of the peritoneum, and even slight retraction of that portion can easily result in its lying intra-abdominally.

In our laboratories, the skin incision for cardiac catheterization in the newborn infant is made parallel to and at the level of the inguinal crease. If balloon septostomy is not contemplated, the catheter is inserted into the long saphenous vein or the saphenous bulb. If transposition of the great arteries is considered a possibility, the catheter is usually inserted into the saphenous bulb close to the saphenofemoral junction (Fig. 1). The vein at this level is usually large enough to accommodate a No. 5.5 or 6.5 French balloon catheter. If the saphenous bulb is too small to admit the desired balloon catheter, however, the catheter is inserted into the femoral vein just caudal to the saphenofemoral junction and the bulb and its tributaries are left undisturbed. The vessel at this point is large enough and, even though it may have to be ligated after the procedure, collateral channels by way of the long saphenous vein and its branches will allow blood flow to bypass this obstruction and to enter the femoral vein downstream to it. When either the saphenous bulb or femoral vein is used, an attempt is made to repair the vessel after removal of the catheters. Even if this results in some degree of narrowing of the vein at the site of catheterization, flow into the common femoral vein will remain relatively free. The resulting patency of the vein should permit its possible use for percutaneous catheterization in the future.

Another advantage of insertion of the catheter at or near the saphenofemoral junction is the ability to control the bleeding and to identify the proximal and distal ends of an accidentally severed vessel. In

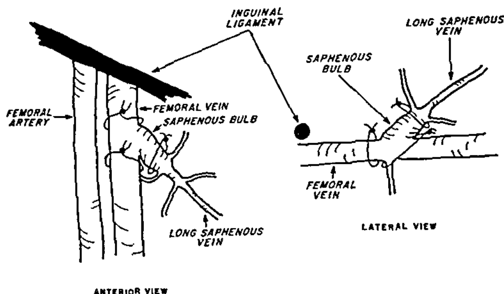


Fig *1* Anatomy of the saphenofemoral venous junction

contrast to the usual saphenous vein cut down in which venous valves prevent back flow and bleeding is easily controlled by traction of the vessel insertion of the catheter into the femoral vein or sapheno femoral junction is accompanied by con siderable bleeding unless preventive mea sures are taken earlier In our laboratories careful dissection and adequate exposure of the femoral triangle including the saphe nous bulb all its tributaries and both proxi mal and distal femoral vein is a standard procedure when a cutdown on the saphe nous bulb or directly on the femoral vein is required Ties are usually placed on the saphenous vein just cephalad to the en trance of the last tributaries and on the femoral vein just proximal and distal to the site of catheter entry (Fig 1) Care is also taken to determine if a deep perforat ing vessel is present in the region to be used Although the site of this vessel is variable if it is present it must be con trolled or the femoral blood flow chan neled into this vessel will cause considerable bleeding into the operative field

If the necessary time and effort are taken for complete exposure of the femoral vein and its branches before the start of the procedure it will be much easier to cop with any difficulties which may aris later on It will be easier to identify and control the end of the vessel in a well-dissected field than to start the dissection in the midst of massive bleeding from a vessel that is accidentally severed during attempts at insertion of the balloon catheter

Diagnostic cardiac catheterization

A number of essential factors have to be ascertained during the initial diagnostic cardiac catheterization in the infant with transposition of the great arteries (see Table 1) The order in which the study will be performed and the extent to which at tempts will be made to obtain the informa tion will of course depend on the clinical condition of the patient In general in addi tion to establishing the primary diagnosis the knowledge of the presence of a hemo dynamically significant ventricular septal defect and/or patent ductus arteriosus is essential for the future management of the patient

The initial phases of cardiac catheteriza tion in infants other than those with TGA are usually accomplished in our labora tories by use of a catheter with an end hole This type of catheter permits the measurement of the pulmonary capillary wedge pressure which is not readily ob tained in newborn infants with TGA Since the left atrium and pulmonary veins will be entered directly the only usefulness of this measurement may be in the assessment of pulmonary venous obstruction In order

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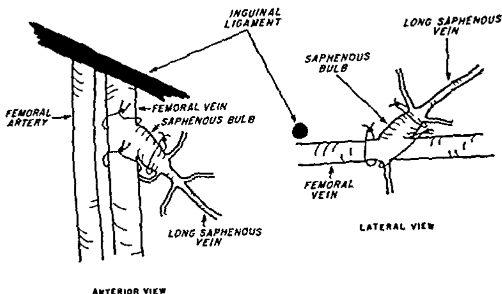


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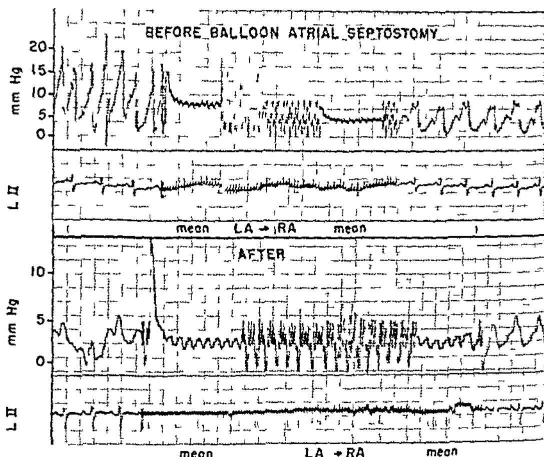


Fig. 2. Left atrium to right atrium withdrawal pressure record.

to eliminate the necessity for a catheter exchange, the initial phases of the procedure are therefore performed with a closed end, side hole (NIH type) catheter, which is better suited for angiocardiography.

Once the catheter has been inserted into the femoral vein and advanced up the inferior vena cava to the right atrium, the first decision has to be made. If the infant is extremely ill and cannot tolerate the few minutes required to make the necessary physiologic measurements, the catheter is passed into the left ventricle. If there is any difficulty in advancing the catheter from left atrium to left ventricle, a guide wire with a curved, stiff end can be inserted into the catheter and advanced to the tip. This will bend the tip of the catheter into the mitral valve, after which the catheter can be advanced over the wire into the left ventricle. Once the catheter is in this chamber, angiocardiography will show filling of the pulmonary artery from the left ventricle, thus establishing the diagnosis of TGA. In some circumstances, this can even be demonstrated by injection of contrast material into the left atrium. In the patient who can tolerate a few physiologic measurements, we prefer to make these before performing angiocardiography in the left side of the heart. The catheter is therefore advanced from right atrium to right ventricle and out into the aorta, where the systemic oxygen saturation is measured. Although this catheter course is suggestive of TGA, a similar course is often seen in patients with tetralogy of Fallot, double outlet right ventricle, and truncus arteriosus. It is therefore the left ventricular injection of contrast material that will easily and quickly distinguish TGA from other anomalies, instead of the time-consuming injections in multiple views that would be required in the right side of the heart.

While the catheter is in the aorta, it is advanced to the distal portion of the arch and an injection of a small amount of contrast material (0.5 ml.) is made in an attempt to determine the presence of a hemodynamically significant ductus ar

teriosus This information may be essential for future management of the patient, since the presence of severe intractable congestive heart failure would be an indication for surgical closure of a large patent ductus arteriosus The catheter is then withdrawn first to the right ventricle and then to the right atrium while pressure and oxygen saturation are measured at various levels

After measurement of the various venous oxygen saturations the catheter is advanced to the left atrium and left ventricle and the studies are completed as outlined above Finally after the diagnosis has been confirmed a withdrawal pressure record is obtained between the left and right atrium This will give a baseline of the phasic and mean pressure differentials between the two atrial chambers before the BAS (Fig 2)

At this point the diagnosis has been established pressure and oxygen saturation have been measured in each of the cardiac chambers and the presence or absence of a hemodynamically significant patent ductus arteriosus has been determined The total time interval from insertion of the catheter to this point should be no more than 15 to 20 minutes When the patient s condition permits further diagnostic studies can be performed prior to BAS However since the oxygen saturation is rather low in most patients particularly those with an intact ventricular septum it is preferable to defer further studies until after the BAS has been performed

Balloon atrial septostomy

The procedural details of balloon atrial septostomy have recently been reviewed[2] but a few important points bear stressing The use of a small hemostat to dilate the vein will often facilitate the introduction of the balloon catheter In those patients in whom even after dilatation it is still not possible to introduce the balloon catheter into the vein slight longitudinal extension of the incision in the saphenous bulb or femoral vein will permit introduction of the catheter

In order to insure that an adequate interatrial communication will be produced by balloon septostomy the first pullback should be performed with a balloon that has been inflated to at least 1 0 cm (about 2 ml of solution) This diameter is about equivalent under fluoroscopy to the width of the infant s vertebral column If smaller volumes are used initially or if the catheter is not withdrawn from the left atrium to the right atrium with a rapid jerking motion the result will be dilatation without tearing of the foramen ovale Although this may produce the desired result initially septostomy will later be found to have been inadequate

Completion of diagnostic procedure

The extent of further investigations after BAS is determined by the condition of the patient If possible an attempt should be made at least to determine the post BAS systemic arterial oxygen saturation and pressure as well as the pressure gradient between the two atrial chambers Studies to determine the presence of a ventricular septal defect or large patent ductus arteriosus should also be performed at this time if they have not been done previously

In most cases the pulmonary artery is entered only after a great deal of catheter manipulation Although the measurement of the pulmonary arterial pressure is essential in subsequent catheterization procedures the amount of time required to obtain this measurement in a small sick infant is usually not warranted unless left ventricular pressure is at or near systemic levels We therefore attempt for a few minutes to pass the catheter into the pulmonary artery and if unsuccessful will defer this measurement to the second catheterization at about 3 to 4 months of age when the patient will be larger and better able to tolerate the increased time in the catheterization laboratory

Vessel repair

Once the diagnostic procedures and BAS have been completed and any further medications such as sodium bicarbonate have been given the catheter is removed An attempt is then made to repair the vein If the saphenous bulb has been the site of catheter entry the main femoral vein channel should remain patent Even if obstruction will result at the site of catheter entry collateral channels from the long saphenous vein are sufficient to bypass this region

If the femoral vein caudal to the saphen

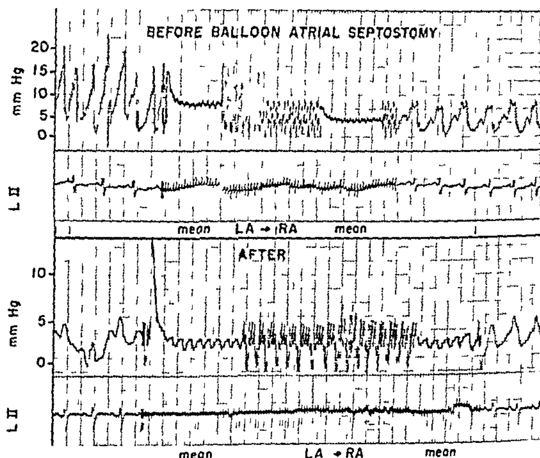


Fig. 2. Left atrium to right atrium withdrawal pressure record.

to eliminate the necessity for a catheter exchange, the initial phases of the procedure are therefore performed with a closed end side hole (NIH type) catheter which is better suited for angiocardiography.

Once the catheter has been inserted into the femoral vein and advanced up the inferior vena cava to the right atrium the first decision has to be made. If the infant is extremely ill and cannot tolerate the few minutes required to make the necessary physiologic measurements the catheter is passed into the left ventricle. If there is any difficulty in advancing the catheter from left atrium to left ventricle a guide wire with a curved, stiff end can be inserted into the catheter and advanced to the tip. This will bend the tip of the catheter into the mitral valve after which the catheter can be advanced over the wire into the left ventricle. Once the catheter is in this chamber, angiocardiography will show filling of the pulmonary artery from the left ventricle, thus establishing the diagnosis of TGA. In some circumstances, this can even be demonstrated by injection of contra material into the left atrium. In the patie who can tolerate a few physiologic measure ments we prefer to make these befo performing angiocardiography in the le side of the heart. The catheter is therefo advanced from right atrium to right ve tricle and out into the aorta, where th systemic oxygen saturation is measure Although this catheter course is sugge of TGA, a similar course is often seen i patients with tetralogy of Fallot, doub outlet right ventricle, and truncus a teriosus. It is therefore the left ventricul injection of contrast material that wi easily and quickly distinguish TGA fro other anomalies instead of the time consuming injections in multiple view that would be required in the right side the heart.

While the catheter is in the aorta it advanced to the distal portion of the arc and an injection of a small amount contrast material (0.5 ml.) is made in a attempt to determine the presence of hemodynamically significant ductus ar

The infant with transposition of the great arteries
II Results of balloon atrial septostomy

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In the infant with transposition of the great arteries (TGA) prompt creation of an atrial septal defect may immediately improve the critically ill patient and is frequently life saving Balloon atrial septostomy (BAS) introduced by Rashkind and Miller[1] in 1966 offers a non-operative means of creating the atrial septal defect in the infant at the time of the initial diagnostic cardiac catheterization This initial procedure may also be sufficient to provide effective long term palliation until the appropriate age for corrective operation This report describes the results of BAS in patients with TGA treated at the Texas Children s Hospital in a 3½ year period

Materials and methods

During the 43 month period from September 1967 to April 1971 BAS was performed in 45 infants with transposition of the great arteries This procedure was carried out early in the course of cardiac catheterization once the diagnosis of TGA had been established

Cardiac catheterization and BAS were performed by way of the right femoral vein or saphenofemoral junction BAS was performed according to the techniques described by Rashkind and Miller[1,2] When the patient s clinical condition permitted oxygen saturations and pressure curves were obtained both before and after BAS Septostomy was attempted in all patients with TGA under 6 months of age with the realization that it was likely to be most effective in the first month of life Even though it can be expected that the most prompt and obvious improvement would occur in patients with TGA and intact ventricular septum (IVS) in whom there was a measurable atrial gradient and significant arterial hypoxemia BAS was performed in all patients despite equal phasic or mean pressures in the right and left atrium and despite relatively high arterial oxygen saturation (i e 75 per cent or more)

The results of the BAS were classified according to the following criteria

1 Good result Rise of systemic oxygen saturation greater than 10 per cent residual

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ous bulb has been the site of catheter entry and it does not remain patent after attempted repair collateral flow through the saphenous channels will bypass this site of obstruction. In contrast to the use of the femoral vein at the level of the inguinal ligament, this segment of the femoral vein downstream from the saphenous bulb will usually remain patent and thus provide a site for future percutaneous cardiac catheterization. This is of considerable importance in the infant with TGA who, if he survives, will ultimately require a number of cardiac catheterization procedures.

Results of BAS

Cardiac catheterization and BAS have been performed in 45 infants with TGA according to the protocol outlined in this paper. Forty-one of these 45 patients (91 per cent) were considered to have had initially successful palliation by this technique. Results in this series of patients are reported in detail in the companion paper.[4]

Thirty-three patients are presently alive from 6 months to 4 years after the initial BAS. Although some patients have required further operative palliation, 27 of the 45 patients (60 per cent) are either alive at this time or had survived to total correction with *BAS* as their *only* palliative procedure.

Summary

A cardiac catheterization protocol for the newborn infant with transposition of the great arteries should eliminate duplicated steps and should enable the performance of a rapidly executed yet efficient, initial diagnostic cardiac catheterization and balloon atrial septostomy. Important areas of consideration include regulation of body temperature, adequate exposure of the femoral vein, the site of catheter insertion, as well as the various diagnostic facets of the cardiac catheterization which will greatly influence the future management of the patient.

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Table II Repeat balloon septostomy in TGA

Patient	Anatomy	Initial septostomy		Repeat septostomy		Subsequent treatment	Late result
		Age	Result	Age	Result		
R R	IVS and PS	2 weeks	G	4 months	U§	BH + Ao – PA shunt	Alive
K A	VSD and PS	5 days	G	9 months	G‡	Mustard operation	Alive
D F	VSD and PS	3 days	G	8 months	G	Medical	Alive
M S	VSD and PS	5 weeks	G	10 months	G	Medical	Alive
T B	Taussig Bing	10 days	G	11 months	U	BH + PA banding	Alive
L S	VSD and PS	8 days	G	2 months	U	BH†	Alive
K C	VSD and PS	1 day	G	2 weeks	U	BH + Ao – PA shunt	Died
M D	IVS and PS	3 days	G	7 months	U	BH	Alive
J M	IVS	1 month	U	3 months	U	BH	Alive

*Small VSD not repaired
†Spontaneous closure of VSD
‡G = Good result
§U = Unsatisfactory result
Successful repeat BAS = 3/9 (33 1/3 per cent)
Abbreviations Ao = aorta BAS = balloon atrial septostomy BH = Blalock Hanlon operation IVS = intact ventricular septum PA = pulmonary artery PS = pulmonary stenosis TGA = transposition of the great arteries VSD = ventricular septal defect

One infant died during attempted BAS as the result of a perforation of the right atrial appendage Three other patients (one with IVS one with VSD and the third with double outlet right ventricle and coarctation) had an unsatisfactory result from BAS

Nine patients have required a second BAS 3 weeks to 11 months after the initial procedure Eight of these were considered to have had a good result from the initial BAS The result of the second septostomy was good in 3 patients (33⅓ per cent) and they have required no further palliative operative treatment These results are summarized in Table II

Six infants exclusive of those who have had a second BAS have required further palliation Two have had a surgical atrial septectomy performed while 3 have required an aorta to pulmonary artery shunt operation because of severe hypoxemic episodes Ligation and division of a large ductus arteriosus was performed in one patient because of severe persistent heart failure Fig 1 illustrates the total number of further palliative procedures that have been performed in patients with TGA following the initial BAS In all 15 of the 44 patients who survived initial BAS have required repeat BAS and/or palliative surgery None of the patients who had palliative surgery has undergone total correction as yet

Thirty patients with TGA have had no palliative procedures performed subsequent to the initial BAS Twenty two of these patients are presently alive 5 patients having undergone total correction Eight patients have died, 2 of these following total correction

A total of 12 deaths has occurred in these 45 patients one of them as a complication of BAS Three deaths occurred during the first week following BAS In each instance progressive clinical deterioration was accompanied by persistent congestive heart failure and considerable alterations of biochemical homeostasis Two of these patients were considered to have had successful septostomies and at post mortem examination were found to have large atrial septal defects There have been 3 deaths which occurred shortly following palliative operations and 2 others attendant to total correction Late deaths have occurred in 3 other patients—one from pneumonia at age 7 months one of congestive heart fail

Table I Immediate results of initial balloon atrial septostomy

Type TGA†	Number of patients	Results		
		Good	Fair	Unsatisfactory
IVS	17	15	0	2
IVS & PS	10	10	0	0
VSD	6	4	1	1
VSD & PS	7	7	0	0
VSD & other anomalies*	5	4	0	1
TOTALS	45	40	1	4

*1 coarctation 2 large PDA 1 Taussig Bing anomaly 1 double outlet right ventricle and coarctation
†Abbreviations IVS = intact ventricular septum PDA = patent ductus arteriosus PS = pulmonary stenosis TGA = transpos of the great arteries VSD = ventricular septal defect

mean atrial pressure gradient of less than 2 mm Hg and significant clinical improvement

2 Fair result Rise of systemic oxygen saturation less than 10 per cent residual mean atrial pressure gradient of less than 4 mm Hg and only slight clinical improvement

3 Unsatisfactory result Absence of rise in systemic oxygen saturation a residual mean atrial pressure gradient of greater than 4 mm Hg and no significant clinical improvement

An effort was made to assess the presence and size of a ventricular septal defect (VSD) ductus arteriosus and to define if pulmonary stenosis (PS) was present

Twenty seven patients were demonstrated to have TGA with IVS Among these patients with IVS, 10 had PS based on a pressure gradient of 10 mm Hg or more between the left ventricle and the main pulmonary artery in the initial or subsequent cardiac catheterizations Eighteen patients had a VSD alone or in combination with other lesions Nine patients were considered to have a small VSD 6 of these on the basis of either the angiocardiographic appearance or a significantly lower pressure in the left ventricle than in the right (20 mm Hg or more difference) Three other patients were considered to have a small VSD despite equal pressures in the two ventricles because of pronounced systemic arterial hypoxemia (below 60 per cent) which improved significantly following BAS Nine patients had a large VSD based on either the angiocardiographic appearance or on equal pressure in the two ventricles and a systemic arterial oxygen saturation greater than 70 per cent Seven patients with VSD had an associated PS while in 5 there were other associated lesions (one with coarctation two with large ductus arteriosus two patients with partial transposition, one with double outlet right ventricle and one with a Taussig Bing anomaly) Patients with TGA and associated stenosis or with atresia of the atrioventricular valves or those patients with a single ventricle (double inlet LV or RV) have been excluded from this study

The age of the patient at the time of the initial cardiac catheterization ranged from 7 hours to 5 months Fifteen patients (per cent) were less than 1 week of age wh a total of 30 patients (68 per cent) were le than 1 month old Weight ranged from 2 kilograms to 5 8 kilograms There was considerable variation in clinical status ho ever all patients with IVS exhibited mo erate to severe degrees of cyanosis Sig and symptoms of congestive heart failu were present in 65 per cent of the patien

Results

Forty four of the 45 infants survived t initial cardiac catheterization Forty-o patients (91 per cent) were considered have had initial improvement from BA The results are summarized in Table

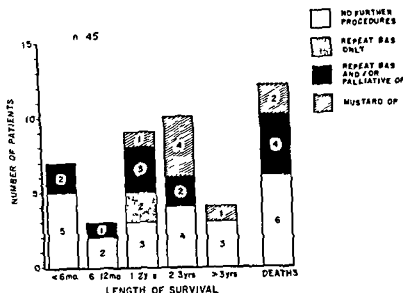


Fig 2 Late results in TGA following BAS *BAS* = balloon atrial septostomy *Op* = operation *TGA* = transposition of the great arteries

Table III *Late results following initial septostomy*

Type TGA	*No operation*	*Palliative* operation*	*Mustard operation*	*Totals*
IVS	8 + (4)	2	1 + (2)	11 + (6)
IVS + PS	3	3 + (2)†	2	8 + (?)
VSD	3 + (1)	—	2‡	5 + (1)
VSD + PS	4	1 + (1)	1*	6 + (1)
VSD + other	1 + (1)	2 + (1)	—	3 + ( )
Totals	19 + (6)	8 + (4)	6 + (?)	33 + (12)

* N p tl nt wl ha l palli tl ye tio h y t nd go total correctl n.
† N mbe p th se d ths.
*Small VSD n t r p d
Abb i tl IVS = i t t t l sept m PS = p lm ry t TGA = t a po tl of tl gr at art ie VSD = ve t icula sept l d fect

the same as those in patients with TGA and VSD (Table III)

Close observation and careful management of the infant with TGA is essential since the early effectiveness of palliative therapy does not necessarily indicate that successful long term palliation has been achieved [8,10] Routine recatheterization during the first year of life has been recommended because of the relative unreliability of conventional clinical parameters in evaluating the hemodynamic status of the patient [11] In the study by Plauth and associates [11] slightly more than half the patients had at least one significant unexpected finding at recatheterization Therefore in addition to frequent clinical re evaluation serial cardiac catheterizations at our institution are now routinely performed in these infants at 4 to 6 months and again between 1 and 2 years of age Evidences of clinical deterioration such as increasing cyanosis hypoxemic spells or congestive heart failure are indications for earlier restudy If an adequate interatrial communication does not exist a second BAS is attempted If indicated surgical palliation is performed In this study 9

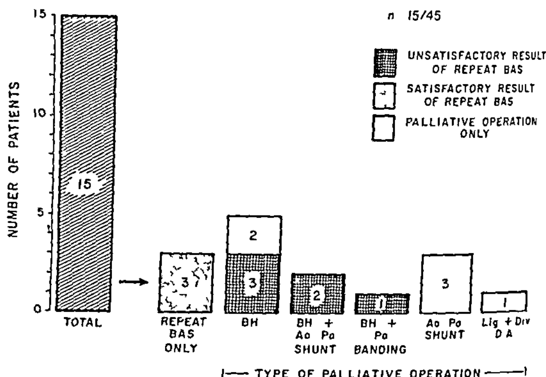


Fig 1 Further palliative procedures in TGA. *Ao* = aorta; *BAS* = balloon atrial septostomy; *BH* = Blalock-Hanlon operation; *DA* = ductus arteriosus; *Pa* = pulmonary artery; *TGA* = transposition of the great arteries.

ure at 2 years of age and one of undetermined cause at 6 months of age.

Thirty three patients are presently alive from 3 to 46 months following the initial BAS (Fig 2). Six patients in this group have had total correction. Of the 27 patients who are alive and have not as yet had total correction, 8 have had palliative surgery, 2 have had a repeat BAS only, and 17 have had no further palliative procedures. Two patients who are alive have had cerebrovascular accidents at 3 and 7 months of age respectively. In the latter patient, this was demonstrated angiographically to be secondary to blockage of the left middle cerebral artery.

Discussion

The introduction of closed surgical atrial septectomy by Blalock and Hanlon[3] in 1950 and the subsequent development of a successful corrective operation by Mustard[4] in 1964 have resulted in a significantly improved prognosis for infants born with TGA. However, in spite of these surgical advances, many critically ill infants were not able to survive the diagnostic cardiac catheterization. For those who did survive this procedure, the mortality from even palliative surgery in early infancy was and still is, over 20 per cent.[6,7]

Balloon atrial septostomy has been shown to be a safe and effective means of immediate palliation in over 70 per cent of infants with TGA.[2,8,10] In this series 41 patients (91 per cent) were considered to have had initially successful palliation by this technique (Table I). Seven of these patients, all with VSD, were considered successful results of BAS in spite of the lack of substantial rise in systemic oxygen saturation. In each instance the initial systemic oxygen saturation was over 70 per cent and the remainder of the criteria for a successful BAS were fulfilled.

Balloon atrial septostomy is of particular importance in the management of the infant with TGA and IVS. Although these infants will be ideal candidates for total correction during childhood, they usually develop marked hypoxemia and congestive heart failure soon after birth. Of 27 patients with TGA and IVS in this study, 93 per cent initially had a good result from BAS (Table I). Seventy per cent of these are presently alive and 60 per cent have not required palliative surgery. The results in patients with TGA and IVS are essentially

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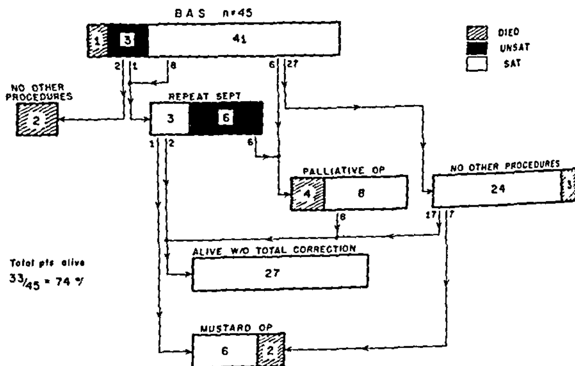


Fig 3 Outcome in 45 patients with transposition of the great arteries following balloon septostomy BAS ... Sept = balloon atrial septostomy Op = operation Sat = satisfactory Unsat = unsatisfactory

patients (20 per cent) have required a repeat BAS (Table II) Of these patients, 3 had a successful repeat septostomy while the remaining 6 patients required subsequent surgical septectomy Twenty seven patients (60 per cent) are either presently alive or survived long enough to undergo total correction with BAS as their only palliative procedure (Fig 3)

The over all mortality rate in this series of 45 patients is 26 per cent One death (2 per cent) was directly related to BAS There were 5 surgical deaths (11 per cent)—2 following Mustard operation (4 per cent) —and 6 deaths unrelated to surgery (13 per cent) Three of the latter occurred during the first week following BAS

This study has demonstrated that BAS is an effective means of providing immediate as well as long term palliation in infants with TCA The results of Barratt Boyes Simpson, and Neutze,[1] using deep hypothermia and limited cardiopulmonary by pass indicate the feasibility of total correction of TGA in early infancy following BAS In other centers where hypothermia technique is not as yet in use a few patients may still require a palliative operation prior to total correction In either case patients following BAS are much less critically ill at the time of operation, have had the opportunity to grow larger in size, an are more likely to survive the surgic procedure

Summary

Balloon atrial septostomy was an effe tive means of immediate palliation in ... per cent of 45 infants with transposition the great arteries There was one deat directly related to the septostomy Th over all survival rate in this series was ... per cent including survivors of total co rection A total of 27 patients (60 per cen are presently either alive or had surviv until total correction with balloon atri septostomy as their only palliative pr cedure

Addendum

Since the writing of this paper 2 of t patients who have previously only had B ... have successfully undergone total corre tion and 1 additional patient has requir a Blalock Hanlon operation Five new p tients with TGA and IVS have undergo successful BAS and are alive and w 2 to 6 months following the procedure

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Table 1 Details of patients

Case No	Age (yr)	Sex	Tribe	Presentation	Heart weight	Comments	Valves affected
K4	35	M	Ganda	CCF	640	—	M T
K23	11	F	Ganda	Acute Rh H Dis	240	—	A M T P
K31	60	M	Luhya	CCF	360	+ EMF	A M T
K35	56	M	Rwanda	CCF	300	+ SBE	M
K62	18	M	Kiga	CCF	435	+ SBE	A M
K73	18	F	Ganda	Fever	520	+ EMF	A M
K81	48	M	Ganda	SBE	320	—	A
K104	20	M	Hangaza	CCF	450	+ EMF	A M
K108	18	F	Acholi	CCF	480	—	A M
K125	30	M	Ganda	CCF	430	—	M T
K131	15	F	Rwanda	CCF	530	—	M
K136	32	F	Ganda	CCF	680	—	A M T
K149	27	M	Ganda	CCF	550	—	M T
K158	37	F	Dama	CCF	370	—	A M
K160	14	F	Dama	Acute Rh H Dis	500	—	A M T P
K168	48	F	Nagifuma	CCF	450	—	A M T P
K169	14	F	Rwanda	CCF	420	—	A M T
K170	47	M	Ganda	CCF	480	—	A

Abbreviations: A = aortic, M = mitral, T = tricuspid, P = pulmonary, EMF = endomyocardial fibrosis, SBE = subacute bacterial endocarditis, Rh H Dis = rheumatic heart disease, CCF = congestive cardiac failure

graphic enlargements of the plates were made using a Durst 1000 condenser enlarger and 8 by 10 inch rapidoprint paper which was processed on an Agfa Gevaert rapid print processor. Areas of interest were then magnified either on the Durst enlarger or under the microscope.

The atrial portions of the hearts which included the mitral and tricuspid valves were examined macroscopically by cutting across and opening out each valve. The main portions of the coronary arteries were sectioned with a fine scalpel at right angles to their lumen every 1 to 2 mm in order to assess the presence of any disease. Diseased valves were excised for microradiography following which sections of both diseased and normal valves and the apex of the heart were processed by conventional histological techniques. The whole transverse ventricular slices which had been microradiographed were also processed with slices up to 10 cm in width being cut on a sledge microtome after embedding in a mixture of paraffin, dental and beeswax. When necessary all the radiopaque medium in the vessels was removed by immersing the cut section in 10 per cent sequestrene solution at room temperature for about 20 minutes.

Results

The details of the patients in this study, their mode of clinical presentation and their hearts are shown in Table 1.

All patients except four presented in cardiac failure. The four exceptions included one patient with pyrexia of unknown origin, two with signs of acute rheumatic heart disease and one with features of subacute bacterial endocarditis. Signs of the latter disease were also present in two of the patients with cardiac failure. In only a small number of cases was there a definite past history of rheumatic fever and in only a few patients was an antistreptolysin O titer estimated. Consequently in many patients the only absolute criterion of RHD that could be used was the presence of Aschoff nodes in histological sections and these were seen in three hearts. However the remaining hearts otherwise showed the gross and microscopical appearances that are accepted as occurring in RHD.[3] In addition three hearts showed characteristic features of EMF.

The 18 hearts which were from patients with an age range of 11 to 60 years and a median age of 29 years weighed between 300 and 680 Gm with a median weight of 450 Gm. When related to body weight[4]

The microvasculature of heart valves in rheumatic heart disease

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The gross and microscopical appearances of valves in rheumatic heart disease are well known but little attention has been paid to their vascularity. Abnormal vessels can be seen on microscopic examination but knowledge of the manner and extent of the vascularization that occurs in these diseased valves is limited.

In a recent postmortem injection study of hearts of patients who died at the Mulago Hospital, Kampala, Uganda, this vascularization proved of value in distinguishing valves affected by endomyocardial fibrosis (EMF) and rheumatic heart disease (RHD). The valves of 18 hearts with features of this latter disease have been studied in detail and the present paper reports the findings.

Materials and methods

The 18 hearts in this study were part of a larger series of 147 normal and abnormal hearts obtained at random from postmortem examinations of patients who died at the Mulago Hospital, Kampala, Uganda. The technique used in this investigation has been described in detail previously[1] but a few minor modifications have been made and briefly it is as follows: Radiopaque medium† with 4 per cent added gelatin was injected simultaneously into both coronary arteries at a pressure equivalent to the patient's systolic blood pressure, or if this was unknown, at 120 mm. Hg. After fixation the hearts were sectioned on a bacon slicer into uniform 5 mm. thick slices from the apex up to just below the mitral valve. The over-all vascular pattern of these slices was visualized by x-raying on to fine grain film (Microtex, Kodak) using a water-cooled low voltage Machlett x-ray tube; 25 kv. and 20 mA exposures were used for 10 seconds with a tube distance of 64 cm. A 20 minute exposure was used to x-ray the atrial portions of the hearts under water on to Crystallex film (Kodak). To demonstrate the finest vessels, selected ventricular slices were radiographed on Kodak Maximum Resolution plates using the same x-ray tube and exposures of 25 kv. and 10 to 20 mA for 15 to 30 minutes according to the thickness of the slice. The plates were developed for 4 minutes at 68° C. in high contrast developer (Kodak D178) and then were fixed and washed using the recommended procedure. Initial photo-

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†Colorpaque, Pilot Chemical Ltd.

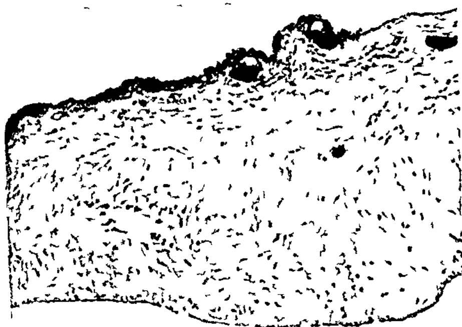


Fig 2 Small vessels along the upper edge of a mitral valve related to the inflamed endocardial surface (Hematoxylin and eosin Original magnification X144)



Fig 3 Inflammatory cell infiltrate mainly in the vascularized upper half of a mitral valve cusp (Hematoxylin and eosin. Original magnification X90)



Fig *1* Microradiograph of a mitral valve with only mild thickening of the cusps showing early vascularization of the cusp from the valve ring (*vr*) *pm* = papillary muscle (Original magnification X4)

14 hearts were considered overweight

All valves were affected in 3 hearts and a further 3 had combined aortic, mitral and tricuspid disease Five hearts had aortic and mitral valves both affected while solitary aortic and mitral valve disease were each seen in two of the hearts

The stage of the RHD and the severity of the involvement of valves varied One heart with all the valves affected was from a patient who died with acute rheumatic fever There was only minor thickening of the cusps of the mitral valve of this heart but the microradiograph showed early vascularization with small vessels extending into it at the valve ring (Fig 1) Histology showed that in early involvement vessels are present along the upper edge of the valve (Fig 2) related to the inflamed endocardial surface and that later there may be an associated inflammatory cell infiltrate (Fig 3) No Aschoff nodes were seen in this valve but they were abundant in the myocardium combined with an acute on chronic inflammatory cell infiltrate

In the more severely affected valves the vascularity becomes markedly increased as shown in a transverse ventricular slice at the level of the mitral valve from a heart of an 11 year old child with active RHD (Fig 4) Examination of the valve ring (Fig 5) shows that the abnormal arteries arise in the subendocardial zone and pass into the valve where they form a dense network without any obvious pattern although on histological examination they resemble capillary like vessels in granulation tissue in some places (Fig 6) Even at this stage the vessels are confined mainly to the upper half of the valve and are still thin walled however, in hearts with longer standing RHD the walls were seen to be thicker and prominent Ten mitral valves of hearts in this series showed severe stenosis with markedly thickened, shortened and fibrotic chordae tendineae The external view of the excised half section of one of these valves is seen in Fig 7 In contrast to normal valves and those involved in EMF the vascularity of these chordae (Fig 8) is marked, with vessels passing up from the papillary muscle and down from the valve ring The network of vessels within this fibrotic mass is irregular with vessels both within the chordae themselves and in the surrounding fibrous tissue

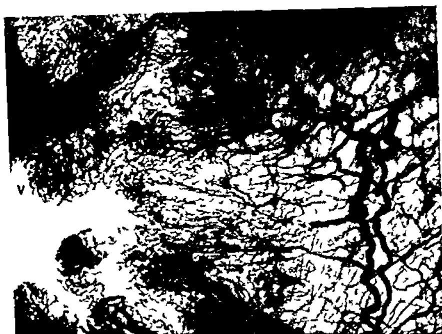


Fig 5 Hi h magnif cat on of the mitral valve (v) illustrated in Fi 4 showin abnormal arteries ari in in the subendocardial zone and pas in out to form a dense network of ves els in the valve (Or inal ma nif cation X11)



Fig 6 Capillary like vessels in the distal part of a mitral valve moderately affected by rheumatic heart di ease (Hematoxyl n and eosin. Original magnification X75)



Fig. 4. Microradiograph of a mid ventricular slice of the heart of an 11 year old child with active rheumatic heart disease showing the markedly vascular mitral valve (v). (Original magnification ×1.5.)

Despite the extensive disease of these chordae they were not bound down to the myocardial endocardium.

The vascularity of diseased aortic valves in this series of hearts was never prominent but many were severely calcified. The majority of tricuspid valves affected by RHD showed only mild disease which was associated with moderate vascularity. Small vessels entered the valve ring and gave delicate branches to the leaflets in a similar manner to the mitral valve. Single small arteries were also seen passing upwards from the papillary muscles into the chordae (Fig. 9).

Two of the three involved pulmonary valves showed only microscopic evidence of disease but the third, in a heart with all the valves affected, showed generalized slight thickening of the cusps with mild fusion at the commissures. The microradiograph of this valve (Fig. 10) showed a fairly dense collection of small arteries within the commissures and a number of vessels giving branches to the valve leaflets.

Discussion

The injection technique used in this and previous studies by the authors has never shown small blood vessels in "normal" heart valves, even when the radiopaque injection medium has filled myocardial capillaries. Few vessels are seen normally in the valve ring although they are present if a small portion of muscle extends down from the myocardium into the proximal part of the valve. Vascularization of valves has only been demonstrated in primary valve disease such as RHD, acute bacterial endocarditis, and non specific inflammation. This is in agreement with Koletsky[5] who concluded in a study of 15 hearts that mitral valves with diffuse gross vascularity almost uniformly showed microscopic stigma of inflammatory disease. In general, however, it is difficult to compare the findings of other workers who have studied the vascularity of heart valves as many different injection media have been used. The percentage of normal valves containing vessels has varied from 2 per cent with $BaSO_4$-gelatin[6] to 48 per cent with Indian ink.[7] More recently, Clarke,[8] using Micropaque, found vessels in 10 per cent of mitral and 16 per cent of tricuspid valves but illustrations showed only scanty vessels in the proximal part of the valve.

The present study has shown that hear

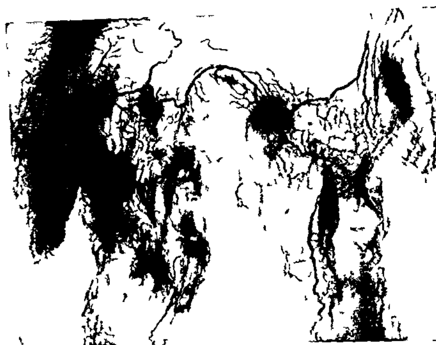


Fig 8 Microradiograph of the valve section in Fig 7 showing the marked vascularity of the thickened fibrotic chordae tendinae. (Original magnification X4 5)



Fig 9 Microradiograph of a mildly diseased tricuspid valve with small arteries entering the valve via the chordae tendineae (c) as well as at the valve ring (vr) (Original magnification X2)



Fig. 7 External view of excised half section of a severely diseased stenotic mitral valve showing markedly thickened, shortened and fibrotic chordae tendineae (Original magnification X4.)

valves are vascularized early in the course of RHD. In the atrioventricular valves vessels initially enter at the valve ring, pass down close to the upper surface of the valve and are seen in association with deposits of fibrin on the endothelial surface. The larger vessels extend down the fibrous extensions of the chordae tendineae from where they send delicate branches into the leaflet of the valve. At the same time small arteries pass up from the papillary muscles into the chordae tendineae and vascularize the lower part of the valve. As the valve disease becomes more florid the density of vessels in the valve increases markedly, but the majority are still confined to the upper half. Initially the inflammatory cell infiltrate may be scanty but usually it extends as the vascularity increases. The blood vessels are thin walled in the early stages and resemble capillary like vessels in some areas but as the valve becomes fibrotic they may become thicker walled. The present study showed that this occurred within the valve as well as at the valve ring, as illustrated by Hudson.[8]

Even at a later stage the severely affected mitral valves retain a fairly extensive network of vessels particularly within the thickened chordae tendineae but as calcification occurs the hearts in this study showed fewer vessels although some may have been obscured on the microradiographs by the calcification. Calcification may also be the reason for the demonstra

Uganda has been studied using injection microradiographic and histological techniques In mildly diseased atrioventricular valves small vessels were first seen at the valve ring and along the inflamed endothelial surface of the valve leaflets but vessels also passed up the chordae tendineae to the lower part of the leaflets The density of vessels increased with more florid disease and sometimes the capillary like vessels became thick walled but the vascularity diminished as the valves became fibrotic and calcified In the aortic and pulmonary valves vessels passed into the cusps mainly from the commissures These appearances were of value in distinguishing rheumatic heart valves from avascular normal valves and those affected by endomyocardial fibrosis

This study was carried out with the close co-operation of Professors M S R Hutt and R A B Drury and we are extremely grateful to them and to Professors K Somers and G Dick and to Drs A G Shaper and A Pomerance for their constant advice and helpful criticism We thank the many physicians and pathologists who provided material Professor A C Thackray for assisting with the histological photographs and Mrs I D James Mrs I Steiner Mrs R Coles Miss E Mos and Miss J Whittingham for their technical help This work was supported by a grant from the British Heart Foundation

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Fig. *10* Microradiograph of a mildly thickened pulmonary valve showing a fairly dense vascular pattern in the commissures (*c*) with vessel giving branches to the valve leaflets (Original magnification X4)

tion of few vessels in the diseased aortic valves The process of vascularity of the tricuspid valve was similar to that of the mitral valve but was never as extensive as the severity of disease was usually considerably less

Pulmonary valve involvement in rheumatic disease is rarely obvious macroscopically but in this study this valve showed vascularization in three hearts The small vessels are initially confined to the valve ring but later enter the commissures and branch out to give a fine network of vessels throughout the cusps

The vascularity of the valves in RHD has proved of value in distinguishing this disease from EMF In EMF the valve itself is not primarily diseased but becomes involved secondarily by encroaching thrombus, and at no time do the valves in this condition become vascularized Any vessels seen on histological section to be close to the valve in EMF are present in the organizing thrombus [9] In addition in EMF the chordae tendineae are bound down to the myocardial endocardium and fibrosis obliterates the sharp inferior junction of the valves with the myocardial wall [9] whereas in RHD the chordae tendineae become thickened and distorted but are not tethered and the junction described above is sharp The distribution of the disease with EMF usually affecting only the posterior cusp of the mitral valve the posterior and septal cusps of the tricuspid valve, and very occasionally the pulmonary valves is useful in distinguishing from the generally accepted distribution of rheumatic heart valve disease [3] In addition stenosis of valves does not occur in EMF whereas it is common in RHD

The combination of EMF and RHD in three of the 18 hearts in this study is a greater incidence than would be expected in a random series of hearts from patients dying at the Mulago Hospital Kampala Uganda as shown by Shaper Hutt and Coles [10] and is in agreement with the findings of these workers in their analysis of postmortem investigations over the period 1950 to 1965 at the same hospital

Summary

The process of vascularization of the valves of 18 hearts with features of rheumatic heart disease which were part of a larger series of 147 hearts from patients who died at the Mulago Hospital, Kampala

Uganda has been studied using injection microradiographic and histological techniques In mildly diseased atrioventricular valves small vessels were first seen at the valve ring and along the inflamed endothelial surface of the valve leaflets but vessels also passed up the chordae tendineae into the lower part of the leaflets The density of vessels increased with more florid disease and sometimes the capillary like vessels became thick walled but the vascularity diminished as the valves became fibrotic and calcified In the aortic and pulmonary valves vessels passed into the cusps mainly from the commissures These appearances were of value in distinguishing rheumatic heart valves from avascular normal valves and those affected by endomyocardial fibrosis

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The vectorcardiogram and electrocardiogram in supravalvular aortic stenosis and coarctation of the aorta

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Since Williams, Barratt-Boyes, and Lowe[1] described four patients with the syndrome of supravalvular aortic stenosis (SAS), peculiar facies, and mental retardation, great interest has been focused on this entity.[2-5] Very little has been reported, however, on the electrocardiographic (ECG) and vectorcardiographic (VCG) findings in this condition.

In a review of the VCG's in patients with SAS, we have noticed a characteristic transverse plane QRS loop configuration. Similar QRS changes were also seen in patients with isolated coarctation of the aorta, although with less frequency.

The purpose of the paper is to present 29 patients with obstruction of left ventricular ejection distal to the aortic valve, including 8 cases of SAS and 21 cases of aortic coarctation.

Methods

The diagnosis in the eight cases of SAS was proved by cardiac catheterization and/or aortography. Their pulmonary angiograms and/or pressures in the right ventricle were normal. All had classic clinical features of the syndrome described by Williams, Barratt-Boyes, and Lowe.[1]

Twenty patients with discrete thoracic coarctation (distal to the origin of the left subclavian artery) and one patient with abdominal coarctation were studied. The lesions were documented by aortography, surgery, or both.

The Frank[6] system of VCG lead placement was used. The chest electrodes were located at the level of the intersection of the sternal borders and the fifth intercostal space. Routine scalar ECG's were taken on all patients.

The following VCG analyses were done in the transverse plane: angles and magnitudes of the 0.01 second, 0.02 second, and maximum QRS vectors; magnitude of the maximum late rightward QRS forces (Sx); angle and magnitude of the maximum T vector; duration of the QRS loop; direction of inscription of the QRS and T loops. The angle of the maximum QRS vector and the direction of inscription of the QRS loop in the frontal plane were also determined. The angular notation as proposed by Helm[7] was used.

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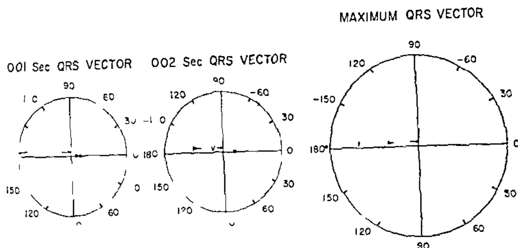


Fig 1 Scattergrams depicting the direction and magnitude of the 0 01 0 02 second and the maximum QRS vector in the transverse plane vectorcardiogram of eight patients with supravalvular aortic stenosis.

Table I Data in patients presenting with supravalvular aortic stenosis

Patient	1	2	3	4	5	6	7	8
Age (yr)	15	4	16	5	5	14	6	12
Sex	F	F	M	F	F	F	F	M
Gradient across stenosis (systolic) mm. Hg		*	81	21	55	27	80	65
Transverse plane VCG								
Max. QRS vector								
angle (degrees)	−120	−155	−100	−145	−100	−100	−115	+15
magnitude (mv)	1 6	1 0	2 2	1 4	2 0	0 7	2 1	1 5
time (sec)	0 040	0 048	0 042	0 034	0 032	0 040	0 032	0 026
0 01 sec QRS vector								
angle (degrees)	+75	0°	+75	0°	+85	+115	+32	+25
magnitude (mv)	0 20	0 10	0 40	0 10	0 5	0 20	0 50	0 30
0 02 sec. QRS vector								
angle (degrees)	+45	+60	+30	+26	+50	+50	0°	+38
magnitude (mv)	0 3	1 0	0 8	1 0	1 2	0 5	0 4	0 8
Max. late rightward QRS forces (mv)	0 7	0 9	0 45	1 2	0 3	0 1	0 9	0 1
Total QRS duration (sec.)	0 08	0 054	0 062	0 060	0 060	0 064	0 06	0 054
Maximum T vector								
angle	+25	−43	+90	+70			+35	+25
magnitude	0 1	0 2	0 3	0 3	0 2		0 5	0 3
Frontal plane QRS loop								
Angle of maximum vector	+60	+52	+110	+155	+45	+60	+180	+50
Direction of inscription	CW†	CW	CW	CW	CW	CW	CW	CW
ECG	N†	N	LVH†	N	N	N	N	N

* Diagnosis by [illegible]graphy
† Abbreviations LVH = left ventricular hypertrophy N = normal CW = clockwise

Results

Supravalvular aortic stenosis The pertinent findings in patients with SAS are summarized in Table I The age of the patients ranged from 4 to 16 years There were 6 girls and 2 boys The peak systolic gradient across the stenotic area obtained in six of the patients varied from 21 to 81 mm Hg

Fig 1 depicts the magnitude and direction of the 0 01 0 02 second and maximum QRS vectors in the transverse plane The

Table II Data in patients presenting with coarctation of the aorta

Patient	1	2	3	4	5	6	7	8	[illegible]
Age (yr)	8	10	20	7	12	9	10	8	[illegible]
Sex	F	F	M	M	M	M	M	F	[illegible]
Documentation	S*	S	S	S	A* S	S	A	A	[illegible]
Transverse plane VCG									
Max. QRS vector									
angle (degrees)	−105	−101	−130	−122	−127	−106	−103	−95	
magnitude (mv)	2.1	2.1	1.5	2.1	1.7	1.7	2.?	1.?	[illegible]
time (sec)	0.042	0.048	0.044	0.044	0.040	0.038	0.038	0.0?6	[illegible]
0.01 sec. QRS vector									
angle	+50	+90	+48	+64	+80	+78	+35	+??	[illegible]
magnitude	0.40	0.50	0.25	0.40	0.20	0.40	0.40	0.40	[illegible]
0.02 sec. QRS vector									
angle	+12	+70	0	+28	+52	+43	+23	−6	
magnitude	1.2	1.0	0.6	1.2	0.6	0.8	1.2	0.9	[illegible]
Max. late rightward QRS forces (mv)	0.5	0.4	0.9	1.1	1.1	0.6	0.5	0.3	[illegible]
Total QRS duration	0.068	0.08	0.096	0.070	0.062	0.06	0.064	0.054	[illegible]
Maximum T vector									
angle	+7	0	+30	0	0	+?0	+2?	0	
magnitude	0.6	0.4	0.3	0.4	0.4	0.4	0.4	0.3	[illegible]
Frontal plane QRS loop									
Angle of maximum vector	+28	+45	−176°	+10	+140	+55	0	+50	
Direction of inscription	CW*	CW	CW	CW	CW	CW	CW	CW	[illegible]
ECG	N*	N	N	N	rsR V_{4R}	N	N	N	[illegible]

*Abbreviation: S = surgery; A = aortography; C = cardiac catheterization; LVH = left ventricular hypertrophy; CW = clockwise
† Abdominal coarctation

magnitude of the 0.01 second QRS vector was within normal limits.[8]* In 7 of 8 patients this vector was directed leftward or leftward and anteriorly, 4 of which are outside the normal range. The magnitude of the 0.02 second QRS vector was normal in all except one, which was abnormally large. The direction of the vectors was normal in all cases. The magnitude of the maximum QRS vector was normal in all patients. However, the vector was displaced posteriorly and rightward in 7 of the patients, which was distinctly abnormal.[8,9] The magnitude of the maximum late rightward QRS forces, which is the equivalent of the S wave in the orthogonal lead X (Sx), was abnormally large in 4 cases.[10] This finding was correlated with a rather deep S wave in lead V_6 of the scalar ECG.

The direction of inscription of the QRS loop was counterclockwise in the transverse plane and clockwise in the frontal plane in all cases. In the frontal plane the loop was wide in 7 of the 8 patients because of prominent mid and late QRS vectors directed inferiorly and rightward.

Routine scalar ECG's were within normal limits in 7 patients. In one it was suggestive of left ventricular hypertrophy because of high voltage of the QRS complexes.

Two of the representative cases are illustrated in Figs. 2 and 3.

Coarctation of aorta

The essential data in patients with coarctation of aorta are listed in Table II. The age of the patients varied from 6 to 20 years. There were 9 females and 12 males. The magnitude and direction of the 0.01, 0.02 second, and maximum QRS vectors in the transverse plane are illustrated in Fig. 4. The magnitude of 0.01 second QRS vector was increased in two cases and its direction was leftward in ten, even though only one was outside the normal limits. The magnitude of 0.02 second vector was increased in 4 patients. The direction of the

*Normal values:
Magnitude = 0.01 sec.—mean 0.29 mv., S.D. ± 0.11
0.02 sec.—mean 0.57 mv., S.D. ± 0.5
maximum QRS—mean 1.3 mv., S.D. ± 0.45
Direction = 0.01 sec.—mean 100.7, S.D. ± 27
0.02 sec.—mean 50°, S.D. ± 28
maximum QRS—mean −8, S.D. ± 36

11 9 M S	12 10 F C A	13 9 M A	14 9 F S	15 7 M C A	16† 14 M A	17 11 I S	18 8 F S A	19 6 M A S	20 11 F S	21 17 M \ S
+5 1 2 0 05	−45 1 5 0 036	−70 1 5 0 036	−68 1 4 0 04	+16 2 0 0 078	−3 1 3 0 038	+6 1 6 0 036	−18 1 5 0 04	−4 3 0 0 034	−70 2 1 0 036	−55 2 4 0 05
+113 0 20	+110 0 25	+97 0 35	+77 0 40	+90 0 30	+137 0 70	+108 0 25	+72 0 10	+118 0 60	+138 0 60	+84 0 75
+45 0 6 0 6	+25 0 6 0 4	+35 1 0 0 2	+48 0 6 0 1	+46 1 2 0 7	+72 0 80 0 2	+50 0 80 0 10	+28 0 6 0 1	+40 0 8 0 4	+30 0 8 0 4	+44 0 60 0
0 090	0 066	0 060	0 070	0 04	0 068	0 056	0 064	0 07	0 07	0 068
−16 0 0	−45 0 1	−10 0 4	−67 0 4		+60 0 3	−15 0 35	0 0 1	0 0 6	−60 0 3	+67 0 4
0 CW r R V R	+57 CW N	+58 CW N	+32 8 N	+22 CCW N	+60 8 N	+47 CCW N	+38 CW N	+78 CW N	+30 8 N	+43 CCW N

erclock ise 8 = f g re f e ght N = normal

vector was normal in all The magnitude of the maximum QRS vector was normal except in one patient where it was increased In 10 of the 21 cases there was a posterior and rightward displacement of this vector with the direction being −90 or farther to the right The magnitude of the maximum late rightward forces (Sx) was abnormally large in four patients

The QRS loop was inscribed counterclockwise in the transverse plane in all patients and it was inscribed clockwise in the frontal plane in 13 Seven of the latter group had a wide loop because of prominent mid or late QRS vectors in the inferior and rightward direction

The ECG s were within normal limits in all except one patient who showed left ventricular hypertrophy by voltage criteria Two patients showed an rSR pattern in V4R One of the patients did not have any evidence of right bundle block in the VCG but there was a rightward and posterior displacement of the QRS loop in the transverse plane (Fig 5) The rightward forces in this patient were more pronounced than in most of the other cases with coarctation of aorta The other patient with this pattern did have a discrete slowly inscribed appendage in the right posterior quadrant of the transverse QRS loop

Discussion

ECG s in SAS have been reported as normal showing left ventricular hypertrophy or right ventricular hypertrophy when there is associated peripheral pulmonic stenosis [11 1]

VCG studies in SAS are few Jue Noren, and Anderson[16] described terminal rightward and posterior forces of the transverse plane QRS loop in one patient with SAS In their case cardiac catheterization revealed normal left ventricular and aortic pressures but right ventricular pressure was 40/8 mm Hg Several areas of stenosis of the right pulmonary artery were detected angiographically In the present series no abnormalities of the right side of the heart were noted at catheterization The frequent association of peripheral pulmonary artery stenosis with SAS necessitates right sided studies in these patients [14 17 18]

Table II Data in patients presenting with coarctation of the aorta

Patient	1	2	3	4	5	6	7	8	[illegible]
Age (yr)	8	10	20	7	1?	9	10	8	
Sex	F	F	M	M	M	M	M	F	
Documentation	S*	S	S	S	A* S	S	A	A	
Transverse plane VCG									
Max QRS vector									
angle (degrees)	−105	−101	−130	−122	−127	−106	−103	−9[illegible]	
magnitude (mv)	2.1	2.1	1.5	2.1	1.7	1.[illegible]	?.2	1.[illegible]	
time (sec)	0.04?	0.048	0.044	0.044	0.040	0.038	0.0?8	0.0?5	[illegible]
0.01 sec QRS vector									
angle	+50	+90	+48	+64	+80	+?8	+35	+?	
magnitude	0.40	0.50	0.25	0.40	0.20	0.40	0.40	0.4?	[illegible]
0.02 sec QRS vector									
angle	+12	+70	0	+28	+52	+43	+?3	−6	
magnitude	1.2	1.0	0.6	1.2	0.6	0.8	1.?	0.9	[illegible]
Max late rightward QRS forces (mv)	0.5	0.4	0.9	1.1	1.1	0.6	0.5	0.3	[illegible]
Total QRS duration	0.068	0.08	0.096	0.070	0.06?	0.06	0.064	0.0?4	[illegible]
Maximum T vector									
angle	+7	0	+30	0	0°	+20	+??	0	[illegible]
magnitude	0.6	0.4	0.3	0.4	0.4	0.4	0.4	0.3	[illegible]
Frontal plane QRS loop									
Angle of maximum vector	+28	+45	−176	+10	+140	+55	0	+50	[illegible]
Direction of inscription	CW	CW	CW	CW	CW	CW	CW	CW	[illegible]
ECG	N*	N	N	N	rsR V₄R	N	N	N	[illegible]

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† Abdominal coarctation

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0.02 sec — mean 0.57 mv S.D. ± 0.25
maximum QRS — mean 1.3 mv S.D. ± 0.45
Direction = 0.01 sec — mean 100.7 S.D. ± 27
0.02 sec — mean 50 S.D. ± 28
maximum QRS — mean −8 S.D. ± 36

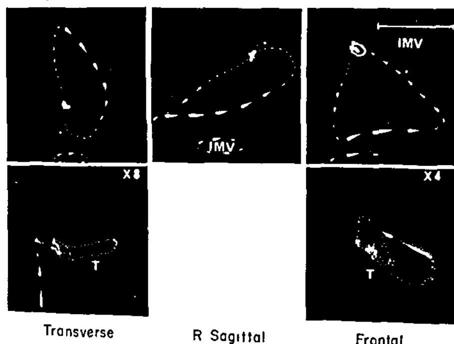


Fig 3A The vectorcardiogram of a 5 year old girl with supravalvular aortic stenosis (Case 5)

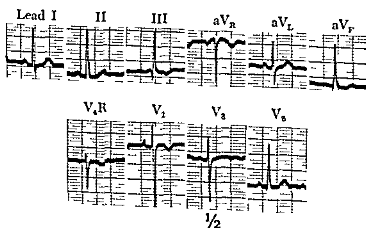


Fig 3B The electrocardiogram of the same 5 year old girl as presented in Fig 3A (Case 5)

cases Ten of 21 cases of coarctation of the aorta had a similar transverse plane loop This was reflected in the ECG s in some although in fewer instances by deep S waves in the left precordial leads These VCG and ECG changes are often seen in patients with right or combined ventricular hypertrophy

Associated with the displacement of the maximum transverse QRS vector was a tendency for the initial forces to be directed leftward Although in many instances the

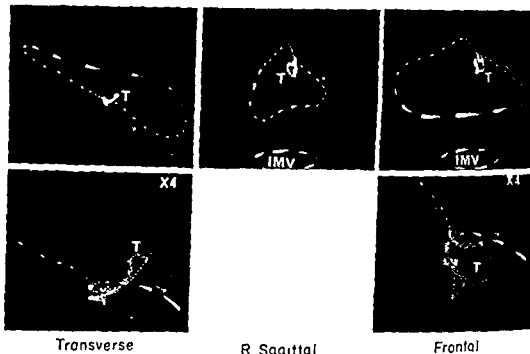


Fig 2A The vectorcardiogram of a 5 year old girl with supravalvular aortic stenosis (Case 4)

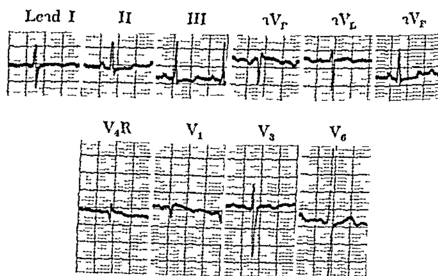


Fig 2B The electrocardiogram of the same 5 year old girl as presented in Fig 2A (Case 4)

Keith, Rowe, and Vlad[19] described left ventricular hypertrophy in 21 per cent of patients over one year of age with coarctation of the aorta. Twelve per cent had normal ECGs, 3 per cent had right ventricular hypertrophy, and 14 per cent had combined ventricular hypertrophy. In their series VCG findings were not described and such information is very limited in the literature. One text described the QRS loop in the transverse plane as havin normal initial inscription but then bein directed abnormally rightward and po teriorly.[20]

In our present study the most character istic VCG finding in patients with SAS wa the displacement of the transverse QRS loop rightward and posteriorly. The maxi mum QRS vector in the transverse plane was directed to the right of $-90°$ in 7 of

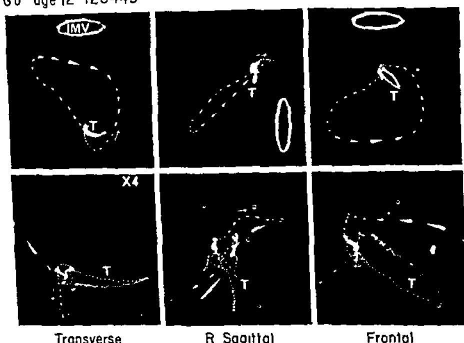


Fig 5A The vectorcardiogram of a 12 year old boy with coarctation of the aorta (Case 5)

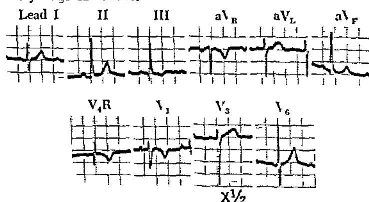


Fig 5B The electrocardiogram of the same 12 year old boy as presented in Fig 5A (Case 5)

block may be either the result of a congenital abnormality of the posterior division of the left bundle branch or due to involvement of the conduction tissue by myocardial fibrosis Such lesions may also account for the previously reported right ventricular hypertrophy or combined ventricular hypertrophy pattern seen in the ECG of patients with isolated coarctation of aorta Confirmation of this hypothesis of course requires detailed examination of the left ventricular conduction system in these patients

The significance of these findings in the interpretation of ECGs in patients with SAS is notable Right ventricular hypertrophy may be erroneously diagnosed (Indeed it would be expected because of the frequent association of the peripheral pulmonic stenosis with this condition)

In coarctation of the aorta an RSR pattern is sometimes seen This may not be

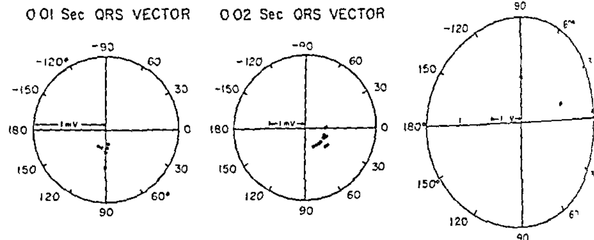


Fig. 4. Scattergrams depicting the direction and magnitude of the 0.01, 0.02 second, and the maximum QR[S] vector in the transverse plane vectorcardiogram in 21 patients with aortic coarctation.

initial vector was still within the normal range, the association of leftward initial forces with rightward terminal vectors presented a rather distinct finding, especially in patients with SAS.

The dominance of right posterior forces was unexpected in patients with obstruction to the left ventricular outflow. For instance, in congenital valvular aortic stenosis the maximum QRS vector in the transverse plane is typically oriented posteriorly and leftward.[21] Right ventricular hypertrophy may be reasonably excluded in the SAS cases by the normal hemodynamic and angiographic findings in the right ventricle and pulmonary arteries. Right sided involvement in apparently isolated coarctation of the aorta would also be unlikely.

Several mechanisms may be proposed to explain the abnormal rightward and posterior displacement of the QRS loop. An extreme clockwise rotation of the heart with left ventricular hypertrophy may shift the posteriorly oriented maximum QRS vector (secondary to LVH) rightward. However, an anatomical basis for such an explanation is lacking. Asymmetrical hypertrophy of the left ventricle may occur with predominant involvement of the posterobasal region of the left ventricle and the posterior portion of the septum. The relatively late left to right activation in the posterior part of the septum may be accompanied by vector forces directed rightward and posteriorly. Detailed examination of autopsied hearts is necessary to verify th[e] hypothesis.

In recent years the concept of left ven[-]tricular hemiblocks has been introduced. In left anterior hemiblock, which is fre[-]quently encountered in both congeni[tal] and acquired heart disease, left axis devi[a]tion is observed. The initial QRS vecto[rs] are directed inferiorly and there is a l[eft]ward and superior displacement of the m[id] and late QRS forces. Left posterior hem[i]block, especially as an isolated abnormalit[y], is reported to be rare. In the frontal pla[ne] VCG the initial QRS forces are directe[d] superiorly and leftward, the QRS loop [is] inscribed clockwise, and the mid and la[te] QRS vectors are oriented inferiorly an[d] rightward. Right axis deviation is obs[erved] in the scalar ECG. The diagnosis can [be] made only in conjunction with clinical i[n]formation as right ventricular hypertroph[y], pulmonary emphysema, vertical heart, a[nd] extensive lateral wall myocardial dama[ge] have to be excluded. Although the front[al] plane QRS axis in the ECG in the patien[ts] studied was within normal limits in mo[st] instances, the VCG did reveal a wide QR[S] loop with prominent inferior and rightwa[rd] forces in many cases, especially those wi[th] SAS. Clinical conditions which may mim[ic] left posterior hemiblock can also be reaso[n]ably excluded in these cases. The rightwar[d] displacement of the mid and late QR[S] forces may likewise explain the posteri[or] and rightward orientation of the transver[se] plane QRS loop. The left posterior hem[i-]

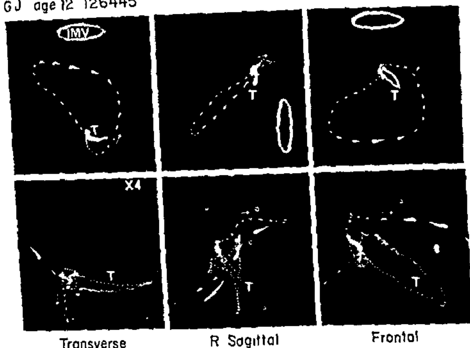


Fig 5A The vectorcardiogram of a 12 year-old boy with coarctation of the aorta (Case 5)

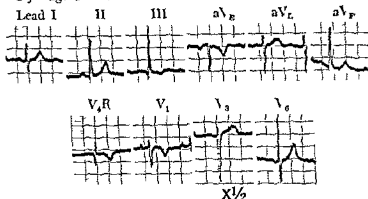


Fig 5B The electrocardiogram of the same 12 year old boy as presented in Fig 5A (Case 5)

block may be either the result of a congenital abnormality of the posterior division of the left bundle branch or due to involvement of the conduction tissue by myocardial *fibrosis* Such lesions may also account for the previously reported *right* ventricular hypertrophy or combined ventricular hypertrophy pattern seen in the ECG of patients with isolated coarctation of aorta Confirmation of this hypothesis of course requires detailed examination of the left ventricular conduction system in these patients

The significance of these findings in the interpretation of ECGs in patients with SAS is notable Right ventricular hypertrophy may be erroneously diagnosed (Indeed it would be expected because of the frequent association of the *peripheral* pulmonic stenosis with this *condition*)

In coarctation of the aorta an RSR pattern is sometimes seen This *may* not be

true right bundle branch block, but rather a reflection of the rightward displacement of the QRS loop

It also seems that a characteristic VCG pattern may be present, especially in patients with SAS. As more patients with this abnormality are fully investigated, the VCG pattern may emerge as a significant diagnostic help

Summary

VCG's were analyzed in 8 cases of isolated supravalvular aortic stenosis (SAS) and 21 patients with aortic coarctation

Seven of 8 patients with SAS and 10 with coarctation had a characteristic transverse plane QRS loop in which the maximum vector was directed rightward and posteriorly

It is postulated that in the absence of demonstrable right sided lesions, this VCG pattern may, in some instances, reflect hypertrophy of the posterobasal portion of the left ventricle or a manifestation of left posterior hemiblock

An electro vectorcardiographic diagnosis of right ventricular hypertrophy may be erroneously made in these patients

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Left ventricular end diastolic pressures following selective coronary arteriography

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Vancouver Canada

Rapid intracardiac injections of radiopaque materials may result in decreased peripheral vascular resistance[1] systemic hypotension[2,3] tachycardia[1,4] or bradycardia[2] increased cardiac output[4] increased pulmonary artery wedge[5] left atrial[1,3,4] and left ventricular end-diastolic[3,4] pressures and an increased plasma osmolality[6] and circulating blood volume[4,7] Maximum changes occur within one to three minutes and values return to preangiographic levels within 15 to 20 minutes[4] Intracoronary injections may result in bradycardia[8] and/or tachycardia[9] hypotension[8] decreased myocardial contractility[8,9] and an increase in left ventricular end-diastolic pressures[10]

Aortic and left ventricular pressures were measured before and at the completion of left ventricular and coronary artery angiography in 40 consecutive patients It is the purpose of this paper to report the changes in left ventricular end-diastolic pressures following angiography to note the abnormal rises of such pressures in diseased hearts and to stress the value of pre and postangiographic pressure measurements in determining the presence of myocardial disease

Methods

The subjects 31 men and 9 women aged 26 to 64 years (mean age 48 7 years) were premedicated with meperidine 100 mg and secobarbital 180 mg Under local anesthesia a size 8F Cordis catheter was introduced percutaneously into the femoral artery and advanced to the left ventricle Aortic and left ventricular pressures were recorded Left ventricular angiography was performed Three minutes later left ventricular and aortic pressures were recorded Coronary arteriography was then performed by the technique of Judkins[11] with a minimum of three views of the left and two of the right being obtained Three minutes following the last injection aortic and left ventricular pressures were again recorded No procedure lasted more than 60 minutes

The contrast material used was diatrizoate methyl glucamine 76 (Renografin 76) 45 ml for the left ventricular angiogram and 10 ml for each coronary angiogram Between 125 and 160 ml of contrast media was used per subject The contrast material was injected into the left ventricle at the rate of 15 ml per second with a Viamonte injector and hand injections sufficed for the coronary angiograms Pressures were recorded with a Statham P32 strain gauge transducer using Electronics for Medicine photographic recording equipment The baseline was at the mid chest level Left ventricular diastolic pressures were divided into early mid and late diastolic pressures (Fig 1) The late end

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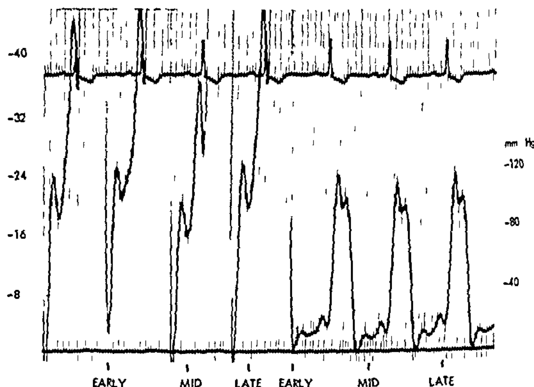


Fig. 1 Left ventricular diastolic pressures at different intensities

diastolic pressure was taken to occur at that point where the left ventricular systolic wave interrupted the atrial transmitted a wave—i.e., 0 052 seconds after the beginning of the Q wave.[1] The height of the atrial kick above the late end diastolic pressure was also recorded

One brief episode of paroxysmal atrial tachycardia and one of atrial fibrillation complicated two investigations and subsided spontaneously Sinus rhythm was present during *all* pressure recordings Angina troubled three patients and cleared with sublingual nitroglycerin Transient hypotension and tachycardia frequently followed ventriculography while bradycardia followed coronary angiography but heart rate and systemic pressures had returned to preangiographic levels at the time of left ventricular pressure recordings (The mean preangiographic heart rate was 70 9 per minute and following angiography it was 76 2 per minute Aortic mean systolic and diastolic pressures before and after angiography were 121 3/69 9 mm Hg and 124 5/69 9 mm Hg)

Results

Of the 40 patients studied 7 (5 men and 2 women with a mean age of 49 years) were considered 'normal' Six were investigated because of atypical chest pain and one because of recurrent bouts of ventricular tachycardia In none did submaximal stress testing produce ischemic electrocardiographic response and the coronary arteries were considered angiographically normal in all Pre and postangiographic heart rate and blood pressure did not vary significantly (Mean heart rate before and after angiography was 80 and 76 per minute Aortic mean systolic and diastolic pressure before and after angiography was 108/67 and 117/67 mm Hg)

The preangiographic left ventricular diastolic pressures were normal in all and averaged 0 mm Hg early 5 3 mm Hg mid and 8 4 mm Hg at late end diastole (Table I) In none did the diastolic pressure rise significantly after angiography and it averaged 0 mm Hg early 5 7 mm Hg mid and 9 2 mm Hg at *late end diastole* The tallest atrial kick to interrupt end diastole was 4 mm Hg *in height*

Thirty one patients were considered by angiography to have coronary artery disease There were 25 men and 6 women with a mean age of 48 7 years Twenty seven were investigated because of angina one because of recurrent ventricular fibrill

Table 1 Left ventricular end diastolic pressures

Patients	No	Mean left ventricular end diastolic pressure (mm Hg)	
		Preangiographic	Postangiographic
Normals	7	8 4	9 2
Single coronary vessel disease	5	10 6	18 4
Double coronary vessel disease	14	17	24 9
Triple coronary vessel disease	9	17 1	27 4

Excluding the three subjects who received nitroglycerin.

on one because of severe congestive failure and two (aged 29 and 34 years) because of previous myocardial infarctions The mean heart rate remained constant at 0 per minute before and after angiography s did aortic pressures (mean systolic and diastolic pressures were 126 7 67 mm Hg before and 126 7/70 mm Hg after angiography) The resting left ventricular diastolic pressures were higher in this group than in the normals (mean early mid and late end-diastolic pressures were 1 4 8 and 15 2 mm Hg) and rose following angiography (to 5 15 3 and 23 mm Hg a rise of 4 6 6 5 and 7 8 mm Hg) Only 4 patients presented no postangiographic rise in left ventricular diastolic pressures and 3 of these had received nitroglycerin during the study following which left ventricular diastolic pressures fell rather than rose

In 14 of the 31 patients with coronary artery disease a prominent atrial kick greater than 5 mm Hg interrupted end diastole and in 5 instances the a wave was greater than 15 mm Hg in height

In general the postangiographic left ventricular diastolic pressure rise was proportionate to the extent of the coronary artery disease All three coronary arteries were diseased in 12 patients Three of these 12 had required nitroglycerin during the study and in these the end-diastolic pressure fell The remaining 9 demonstrated a large rise in early mid and late diastole from a mean of 2 9 and 17 1 mm Hg before angiography to a mean of 4 9 18 1 and 27 4 mm Hg after Two coronary vessels were diseased in 14 patients and mean early mid and late diastolic pressures rose from 1 6 8 and 12 mm Hg to 5 1 14 5 and 24 9 mm Hg A single coronary vessel was diseased in 5 patients and mean pressures rose from 1 4 6 2 and 10 6 mm Hg to 4 8 13 0 and 18 4 mm Hg

Similarly the extent of abnormal myocardium angiographically demonstrated as akinetic or aneurysmal areas paralleled the extent of coronary artery disease and in turn the degree of postangiographic left ventricular diastolic pressure rise Of the 12 patients with the three vessel disease akinetic areas of left ventricular myocardium were present in seven and an aneurysm was present in one Of the 14 patients with two vessel disease akinetic areas were present in eight and an aneurysm in one No abnormality of left ventricular contraction was seen angiographically in the five patients with single vessel disease

Finally two men aged 26 and 49 were considered to have cardiomyopathy and were investigated because of persistent failure The coronary arteries were angiographically normal In both late end diastolic pressures rose in one by 7 mm Hg and in the other by 12 mm Hg much as in the patients with coronary artery disease

Discussion

The cardiovascular response to contrast materials may be the result of the direct action of these materials on the peripheral vascular tree the myocardium or on both Intra-arterial injections of contrast media appear to be toxic to the peripheral vasculature and result in vasodilatation [13,14] The vasodilatation in turn causes skin flushing with the subjective sensation of heat and hypotension which may lead to tachycardia and an increased cardiac output

These manifestations of peripheral vessel toxicity are especially likely to occur if large amounts of media are rapidly and centrally injected and hence dispersed to a wide peripheral bed.[15]

The contrast media may similarly directly affect the myocardium, causing a decrease in ventricular contractility.[9] This may result in bradycardia[8] and in a rise in left ventricular end-diastolic pressure,[10] left atrial pressure,[1,3,4] and pulmonary artery pressure.[3] These direct myocardial effects are most pronounced when concentrated solutions reach the myocardium undiluted, as in coronary arteriography.

Different cardiovascular effects may predominate depending upon which part of the system is most influenced. Hence tachycardia and an increased cardiac output may follow arch aortography when the peripheral vasculature is affected, while bradycardia and a fall in cardiac output may predominate if the myocardium is the prime target as in coronary arteriography. Left ventricular injections may result in varying degrees of myocardial and peripheral vascular effects. In the present study approximately two thirds of the patients who manifested a postcoronary arteriography rise in left ventricular end-diastolic pressure demonstrated no such rise after left ventricular angiography. This suggests that the direct intracoronary injections were more potent in their ability to disturb myocardial function than was the larger but more dilute quantity injected into the left ventricle.

In a search for the toxic factor in contrast media, the volume, hypertonicity, iodine, and sodium content have been implicated. Gootman, Rudolph, and Buckley[3] studied the effects of different contrast agents. They reported that similar volumes of isotonic saline solutions did not significantly disturb those functions studied and concluded that the volume of contrast agent was not the cause of toxicity. They noted minimal cardiovascular responses following injections of 50 per cent glucose solutions, solutions of greater osmolality than sodium iothalamate, which caused the greatest changes, and hence they reasoned that osmolality played little part in toxicity. Gensini and DiGiorgi[16] showed that solutions of equal iodine but varying sodium content produced markedly dissimilar cardiovascular effects, suggesting that sodium and not iodine was the toxic agent.[16] Solutions of increasingly concentrated sodium content produced increasingly severe cardiovascular effects, although methylglucamine may have had a certain protective role.

In the present group of patients investigated, rises in left ventricular end-diastolic pressures occurred after coronary angiography only in those with damaged or ischemic myocardiums—i.e., in those with coronary artery disease or cardiomyopathy and not in the small group of normals. It may be that in cases of narrowed coronary arteries the contrast medium remains in the vessel overly long. Zinner[17] has examined the morphological changes induced in the endothelium by contrast media. He noted endothelial damage, increased permeability, and thrombosis, especially in regions of stasis, as when highly concentrated solutions of contrast media were injected into small arteries. Such conditions of stasis often exist in cases of coronary artery disease with a poor distal runoff. Frequently the contrast medium is seen to remain in a coronary artery well after the injection is completed, and it is in these cases that severe bradycardia with rises in left ventricular diastolic pressure are especially likely to occur. Occasionally myocardial infarction follows such an injection, raising the possibility of endocardial thrombosis, perhaps a result of the toxic effect of the contrast agent.

It has been suggested that angiography be used as a "stress test" to uncover diseased hearts. Gensini and associates[10] reported rises in end-diastolic left ventricular pressures following angiography in patients with coronary artery disease, and Brown and co-workers[18] noted similar rises in patients with aortic stenosis or cardiomyopathy. This present study would confirm the previous observations. No normal patient produced a significant postangiographic rise in left ventricular end-diastolic pressure. All but four of the patients with coronary artery disease produced rises proportional to the degree of the disease. Three of the four not demonstrating a rise had received nitroglycerin, which invalidated the results. The [illegible] nts with

cardiomyopathy also showed a marked postangiographic pressure rise

In another attempt to evaluate left ventricular function following angiography the rate of rise of the intraventricular pressure (dp/dt) was calculated before angiography following left ventricular angiography and following coronary angiography in 13 patients 3 normals and 10 patients with coronary artery disease The results were inconsistent but in general though neither the heart rate nor the aortic diastolic pressure rose (both factors known to increase dp/dt) the rate of rise of the intraventricular pressure rose slightly after coronary angiography This may have been due to the increase in ventricular pre load as a result of the rise in left ventricular end diastolic pressure[19,20] and was not a useful means of differentiating normal from diseased hearts

Summary

Left ventricular pressures were analyzed before and after left ventricular and coronary artery angiography in 40 subjects Seven normal patients demonstrated no rise in left ventricular end diastolic pressure following angiography Two patients with cardiomyopathy and 27 of 31 patients with coronary artery disease demonstrated significant rises in end-diastolic pressure proportional to the extent of the disease following angiography Of the 4 failing to show a rise nitroglycerin had been administered prior to pressure recordings in 3

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Experimental and laboratory reports

The value of the ultrasonic Doppler method and apexcardiography as reference tracings in phonocardiography

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The differentiation between a fourth and a third heart sound or between a third heart sound and an opening snap is of diagnostic and prognostic importance. Although the time relationships of the extra heart sound to the electrocardiogram (ECG) and the aortic second heart sound are usually sufficient for this purpose, additional methods are required in certain instances.[1,2] The most widely used method is the apexcardiogram (ACG).[3-9] However, even the most experienced investigators are unable to obtain satisfactory tracings or accurate correlations in some cases.[4,6,8,11]

The ultrasonic Doppler method was found to be a reliable tool in the study of motion of the left ventricular wall for the timing of the atrial contraction, as well as of the opening and closure of the aortic and mitral valves.[12,15] In a previous communication we demonstrated that distinct signals corresponding to the rapid valvular motion are obtained by this method and that they can be used as a reference point in phonocardiography.[14] The purpose of this communication is to report our experience with this technique in the differential diagnosis of diastolic heart sounds in 67 patients and to compare this method with the ACG.

Principles and methods

The principles of the ultrasonic Doppler method and the apparatus used have been described in detail elsewhere.[13,14] The method is based on the Doppler effect—that is, the apparent change in the frequency of sound when the sound source

From The D[illegible]ion of Cardiology [illegible] and The University of Pennsylvania Medical School at The Philadelphia [illegible] Hospital.
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-r the observer or both move with respect
to each other

Thus when ultrasound emitted from a source on the chest wall is reflected on the moving heart it undergoes a change in frequency (Doppler shift) The Doppler signal which is obtained has a frequency proportional to the velocity of the reflecting structure As the heart contains many structures moving with different velocities the Doppler tracing is a composite of many signals of different frequencies To obtain signals due to the rapid movements of the valves only the signal is processed by a filter favoring high frequencies (corresponding to the velocities of opening and closure of the valves) and excluding low frequencies which are due to the slow movements of the valves and the heart wall

Signals due to the mitral valve movement were obtained by placing the transducer on the fourth left intercostal space about 2 to 3 cm from the sternal border and aiming it in a posterior and slightly medial direction The direction of the transducer was slowly changed until satisfactory signals were obtained and continuous signals due to blood flow were eliminated [14]

The envelope (contour) of the unfiltered Doppler signal obtained with the transducer at the fifth right intercostal space near the sternum was used for timing of the fourth heart sound The presystolic component (a) of this tracing corresponds to the atrial contraction [15]

The ACG was recorded with the patient in the left lateral decubitus position The transducer was placed at the point of maximum impulse as determined by palpation An Electronics for Medicine (E for M) A 167 transducer and FFP amplifiers were used with a band pass filter set between 0 1 and 20 Hz An E for M DR 8 Recorder was utilized

The phonocardiogram was recorded at the point of maximum intensity of the extra heart sound utilizing a Cambridge (Model BM N 21300 4) or a Sanborn (Model 484 10) transducer The band pass filter was set between 170 and 400 Hz Paper speed of 50 or 75 mm per second was used for the recordings Time lines were set at 40 msec for measurement and 1 sec for the illustrations

The patients were unselected and included all those referred for phonocardiography during the period of this study The diagnosis was established by clinical techniques and in most instances verified by cardiac catheterization

Results

1 Timing of the extra heart sound with respect to the aortic second sound The third heart sound occurred 100 to 190 msec after the first major component of the aortic second sound (median 150 msec) The opening snap occurred 60 to 120 msec after the first major component of the aortic second heart sound (median 80 msec) Eight of 25 patients with third heart sound had an A_2S_3 interval below 130 msec which is considered the upper limit for the A_2OS (opening snap) interval [16] One out of 15 patients with opening snap had an A_2OS interval above 100 msec which is considered the low limit for the A_2S_3 interval [17] Thus in nine of the 42 patients the diagnosis of the extra heart sound (ES) could not be made on the basis of A_2ES interval alone (Tables I and II)

2 Relation of the ACG and the mitral opening of the Doppler tracing (MO) to the opening snap In 16 out of 17 patients the opening snap coincided with the Doppler signal due to mitral opening (MO) (Figs 1 and 2) In the seventeenth patient the opening snap preceded the MO by 2 msec The 0 point of the ACG coincided with the opening snap only in four patients (Fig 1) In 10 patients the 0 point of the ACG followed the opening snap by 5 to 20 msec (Fig 2) In three patients with mitral stenosis a satisfactory ACG could not be obtained (Table II)

3 Relation of the ACG and the mitral opening of the Doppler tracing to the S_3 The third heart sound was closely related to the end of the rapid filling wave in 21 of 25 patients (Fig 3) It followed the 0 point by 20 to 100 msec A satisfactory ACG could not be obtained in four of 25 patients The third heart sound followed the MO by 20 to 100 msec (Fig 4 and Table I)

4 Relation of the 0 point of the ACG to the mitral opening of the Doppler tracing In 14 of 21 patients with third heart sound the 0 point of the ACG coincided with the MO of the Doppler tracing In six of the 21 patients the 0 point of the ACG followed

Table I Correlation of the third heart sound to the ACG (O), the Doppler signal due to mitral opening (MO), and the aortic second sound

Case No	Initials age	Diagnosis	HR*	A_2–S_3	A_2–O	A_2–MO	O–S_3	MO–S_3	O–MO
1	I B 35	Pregnancy	88	130	—	70	—	60	—
2	J M 21	Physiological S_3	82	130	80	80	50	50	0
3	J B 30	Myocardiopathy	110	170	120	120	50	50	0
4	G H 45	Mitral insufficiency	70 80	170	130	130	40	40	0
5	A I 60	ASHD CHF†	115	140	90	80	50	60	10
6	J I 18	Physiological S_3	60	140	65	65	75	[illegible]	0
7	K P 26	Mitral insufficiency	80	150	100	95	50	55	5
8	M J 42	Mitral insufficiency	80	160	120	120	40	40	0
9	P C 68	ASHD	75	120	65	60	55	60	5
10	I S 21	Hyperthyroidism	96	160	100	100	60	60	0
11	G B 32	Mitral insufficiency	82	125	80	80	45	45	0
12	Q J 63	ASHD CHF	75	160	—	100	—	60	—
13	I J 18	Physiological S_3	98	160	—	120	—	40	—
14	K S 16	Pregnancy	72	120	60	60	60	60	0
15	B H 17	Pregnancy	68	120	100	100	20	20	0
16	A K 18	Physiological S_3	100	180	—	100	—	80	—
17	J D 20	Physiological S_3	80	100	50	40	50	60	10
18	K M 38	Mitral insufficiency	84	190	120	120	70	70	0
19	R H 15	Aortic insufficiency MI	80	170	80	80	90	90	0
20	B C 18	Physiological S_3	69	130	60	70	70	60	−10
21	A M 45	Myocardiopathy	80	190	130	125	60	65	5
22	M P 39	IHSS MI	80 85	160	120	110	40	50	10
23	I I 21	Myocardiopathy	90	150	90	90	60	60	0
24	K R 31	Myocardiopathy	84	160	100	100	60	60	0
25	P L 22	Hyperthyroidism	114	180	80	80	100	100	0

*HR, Heart rate; A_2, aortic second sound; S_3, third heart sound; O, 0 point of apexcardiogram; MO, mitral opening by Doppler.
†ASHD, arteriosclerotic heart disease; CHF, congestive heart failure; MI, mitral insufficiency.

the MO by 5 to 10 msec. In one patient it preceded the MO by 10 msec (Table I). In four of the 14 cases with mitral stenosis the 0 point of the ACG coincided with the MO of the Doppler tracing (Fig. 1). In 10 of these 14 patients it followed the MO by 5 to 18 msec (Fig. 2 and Table II).

5. *Relation of the electrocardiographic P wave with the fourth heart sound, the ACG and the Doppler signal due to atrial contraction.* The fourth heart sound occurred 100 to 170 msec after the onset of the P wave. The A wave of the ACG occurred 110 to 190 msec after the onset of the P wave (median, 130 msec). The peak A wave (atrial component) of the Doppler tracing occurred 100 to 160 msec after the onset of the P wave (median 120 msec). The fourth heart sound coincided with the A wave of the ACG in seven of 16 patients. In nine of these 16 patients the fourth heart sound preceded the A wave of the ACG by 10 to 40 msec. In four other patients a satisfactory ACG could not be obtained. The A wave of the Doppler tracing coincided with the fourth heart sound in 15 of 20 patients (Fig. 5). In five patients it preceded the fourth heart sound by 20 msec. In 12 of 16 patients the A wave of the Doppler tracing preceded the A wave of the ACG by 10 to 50 msec. In the rest (four) these two deflections coincided (Table III).

Discussion

The differentiation of the diastolic extra heart sounds (opening snap, S_3, S_4) has important diagnostic and prognostic implications. Although it is usually easy to distinguish the acoustic phenomena by auscultation, the question of the exact diagnosis arises in a significant number of patients. In these cases a phonocardiogram may be helpful. Thus the opening snap occurs 30 to 130 msec after the major component of the second heart sound[16] while the third heart sound occurs 100 to 240 msec after

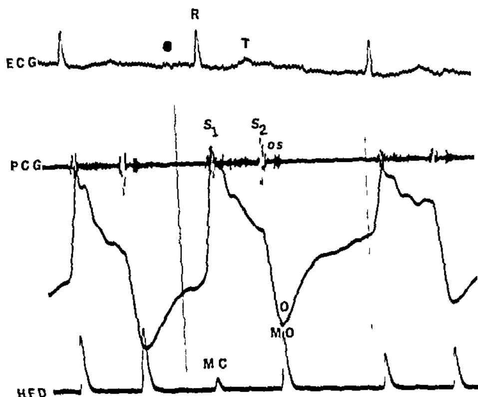


Fig. 1 Mitral stenosis. The 0 point of the ACG (*O*) coincides with the opening snap (*OS*) and the Doppler signal due to mitral opening (*MO*) *HFD* High frequency Doppler tracing Time lines every 1 second

Table II Correlation of the opening snap to the ACG (O) the Doppler signal due to mitral opening (MO) and the aortic second sound

Case No	Initials age	Diagnosis	HR	A_2-OS	A_2-O	A_2-MO	OS O_A	OS MO	MO O
1	H T 37	MS†	65	80	—	80	—	0	—
2	G L 66	MS	72	120	130	120	10	0	10
3	J K 82	MS	82	80	100	82	20	2	18
4	M H 65	MS	86	95	100	95	5	0	5
5	J T 31	MS	84	80	80	80	0	0	0
6	K I 46	MS	70-80	90	95	90	5	0	5
7	J K 28	MS	97	80	80	80	0	0	0
8	J G 36	MS	78	75	—	75	—	0	—
9	J K 21	MS	82	90	100	90	10	0	10
10	K S 27	MS	65	60	60	60	0	0	0
11	P T 43	MS	85	60	70	60	10	0	10
12	J V 35	MS	70	70	80	70	10	0	10
13	G H 28	MS	70	90	95	90	5	0	5
14	F H 42	MS	100-110	60	70	60	10	0	10
15	C J 51	MS	80-90	90	—	90	—	0	—
16	J K 55	MS	95 105	80	85	80	5	0	5
17	M A 65	MS	60-65	88	88	88	0	0	0

HR H rt rat A2 a rtic second sound O 0 po t f pexca dio ram OS ope g s p MO m t al pe g by Doppler
†MS, mitral stenosis.

Table I Correlation of the third heart sound to the ACG (O) the Doppler signal due to mitral opening (MO), and the aortic second sound

Case No	Initials age	Diagnosis	HR*	A_2–S_3	A_2–O	A_2–MO	O–S_3	MO–S_3	O–MO
1	P B 35	Pregnancy	88	130	—	70	—	60	—
2	J M 21	Physiological S_3	82	130	80	80	50	50	0
3	J B 30	Myocardiopathy	110	170	120	120	50	50	0
4	G H 45	Mitral insufficiency	70 80	170	130	130	40	40	0
5	A I 60	ASHD CHF †	115	140	90	80	50	60	10
6	J I 18	Physiological S_3	60	140	65	65	75	75	0
7	K I 26	Mitral insufficiency	80	150	100	95	50	55	5
8	M J 42	Mitral insufficiency	80	160	120	120	40	40	0
9	P G 68	ASHD	75	120	65	60	55	60	5
10	K S 21	Hyperthyroidism	96	160	100	100	60	60	0
11	G R 32	Mitral insufficiency	82	125	80	80	45	45	0
12	Q J 63	ASHD CHF	75	160	—	100	—	60	—
13	I J 18	Physiological S_3	98	160	—	120	—	40	—
14	K S 16	Pregnancy	72	120	60	60	60	60	0
15	B H 17	Pregnancy	68	120	100	100	20	20	0
16	A K 18	Physiological S_3	100	180	—	100	—	80	—
17	J D 20	Physiological S_3	80	100	50	40	50	60	10
18	K M 38	Mitral insufficiency	81	190	120	120	70	70	0
19	R H 15	Aortic insufficiency MI	80	170	80	80	90	90	0
20	B C 18	Physiological S_3	69	130	60	70	70	60	-10
21	A M 45	Myocardiopathy	90	190	130	125	60	65	5
22	M I 39	IHSS MI	80 85	160	120	110	40	50	10
23	I I 21	Myocardiopathy	90	150	90	90	60	60	0
24	K R 34	Myocardiopathy	84	160	100	100	60	60	0
25	I J 22	Hyperthyroidism	114	180	80	80	100	100	0

HR Heart rate A_2 aortic second sound S_3 third heart sound O 0 point of apexcardiogram MO mitral opening by Doppler
† ASHD arteriosclerotic heart disease CHF congestive heart failure MI mitral insufficiency

the MO by 5 to 10 msec In one patient it preceded the MO by 10 msec (Table I) In four of the 14 cases with mitral stenosis the 0 point of the ACG coincided with the MO of the Doppler tracing (Fig 1) In 10 of these 14 patients it followed the MO by 5 to 18 msec (Fig 2 and Table II)

5 *Relation of the electrocardiographic P wave with the fourth heart sound the ACG and the Doppler signal due to atrial contraction* The fourth heart sound occurred 100 to 170 msec after the onset of the P wave The A wave of the ACG occurred 110 to 190 msec after the onset of the P wave (median 130 msec) The peak A wave (atrial component) of the Doppler tracing occurred 100 to 160 msec after the onset of the P wave (median 120 msec) The fourth heart sound coincided with the A wave of the ACG in seven of 16 patients In nine of these 16 patients the fourth heart sound preceded the A wave of the ACG by 10 to 40 msec In four other patients a satisfactory ACG could not be obtained The A wave of the Doppler tracing coincided with the fourth heart sound in 1 20 patients (Fig 5) In five patients preceded the fourth heart sound by 20 ms In 12 of 16 patients the A wave of the Doppler tracing preceded the A wave of the ACG by 10 to 50 msec In the rest (fo these two deflections coincided (Table II

Discussion

The differentiation of the diastolic ex heart sounds (opening snap S_3 S_4) important diagnostic and prognostic im cations Although it is usually easy to d tinguish the acoustic phenomena by ausc tation the question of the exact diagno arises in a significant number of patie In these cases a phonocardiogram may helpful Thus the opening snap occurs to 130 msec after the major component the second heart sound[16] while the th heart sound occurs 100 to 240 msec af

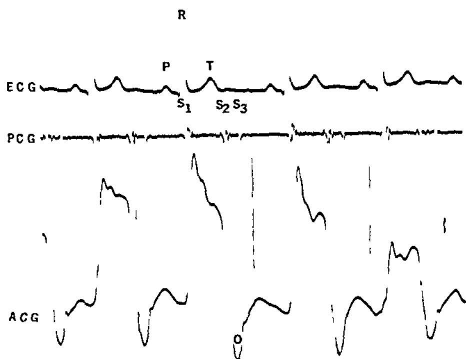


Fig 3 Third heart sound (S_3) The S_3 coincides with the peak of the rapid ventricular filling wave of the ACG

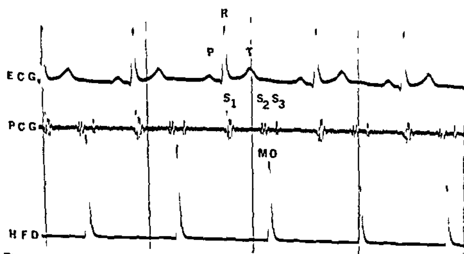


Fig 4 Third heart sound The S_3 follows the Doppler signal of the mitral valve opening (MO) by 60 msec.

valve as previously reported [14] *In addition* the delay in the recording is very small and approximately equal to that of the phonocardiogram The detection of the exact timing of the opening of the mitral valve can also be used for the accurate measurement of the A OS interval which has been utilized as an index of left atrial pressure in subjects with or without mitral *stenosis* [19] Similar results can be obtained by the classical mitral valve echo [15,20] However the method reported here delineates

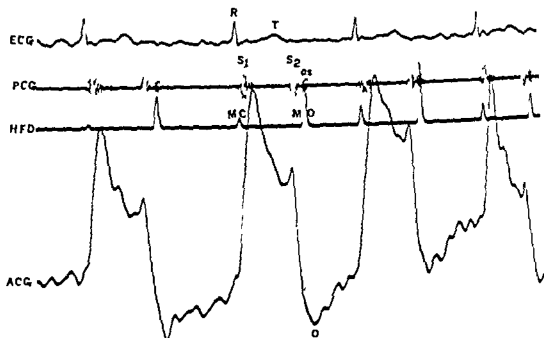


Fig 2 Mitral stenosis The 0 point of the ACG (O) follows the opening snap (OS) by approximately 40 msec The Doppler signal (MO) coincides with the OS

A_2 [17] Since an overlap in these numbers is present the interval between the extra heart sound and the aortic second sound cannot be used as an absolute differential point This is substantiated by the findings of this study Eight of 25 patients with third heart sound had an A S_3 interval below 130 msec and could thus be included in the range of the opening snap while one patient with an opening snap could be classified as an S_3 on the basis of an A OS interval above 100 msec In other cases it is difficult to differentiate a fourth from a third heart sound

Among the reference tracings utilized in the differentiation of these diastolic sounds the ACG is the most popular because of its simplicity in use The A point corresponds to the fourth heart sound the 0 point to the opening snap and the peak of rapid filling wave to the third heart sound (Fig 1) [4] Satisfactory ACG cannot be obtained in the presence of obesity thick muscles, emphysema and pleural or pericardial effusion [4,5] Our experience in this respect is similar to that of Benchimol and co workers [8] who were able to record good tracings in 90 per cent of patients with heart disease We were unable to obtain a satis factory tracing in 11 of 62 patients In other patients distorted tracings can be recorded with faulty positioning of the transducer or air leaks in the recording equipment [4,8,10,11]

In addition to these technical difficulties there is only an approximate relationship between the 0 point of the ACG and the opening snap [8,8,9] While the 0 point of the ACG is related mainly to the end of rapid descent or the nadir of the left ventricular pressure curve [5,8,9] the opening snap occurs at the time of deceleration of the mitral valve during its opening and thus bears a closer relation to the crossing of the left atrial and left ventricular pressure curves [5,18] The Doppler signal due to mitral opening bears an excellent relationship to the opening snap (Figs 1 and 2) In 16 of 17 patients these two phenomena were simultaneous while in the seventeenth patient there was a 2 msec difference In contrast the opening snap preceded the 0 point of the ACG in 10 out of 14 patients by 5 to 20 msec Differences up to 30 msec have been reported by Tavel and associates [5] In an occasional patient this may lead to misinterpretation of an opening snap as a widely split second heart sound (Fig 2)

The excellent correlation of the mitral opening Doppler signal to the opening snap is explained by the fact that the Doppler signal depicts the actual opening of the

Table III *Correlation of the fourth heart sound to the ACG (A) the Doppler signal due to 'rial contraction and P wave of the ECG*

Case No	Initials age	Diagnosis	P S	P A	P 4a p	S-A p	4a-S	4a 4p	4p-S
1	J C 65	ASHD CHF	0 13	0 13	0 11	0	0 02	0 02	0 22
2	L M 52	HCVD	0 11	0 11	0 11	0	0	0	0 26
3	S L 67	ASHD	0 14	0 16	0 12	0 02	0 02	0 04	0 36
4	B J 39	HCVD CHF	0 16	0 19	0 16	0 03	0	0 03	0 18
5	M C 23	Hepatitis	0 10	—	0 10	—	0	—	0 44
6	K J 23	Mitral stenosis	0 10	—	0 10	—	0	—	0 22
7	O L 42	HCDV	0 10	0 13	0 10	0 03	0	0 03	0 24
8	J E 44	Alcoholic myocardiopathy CHF	0 14	0 14	0 12	0	0 22	0 02	0 26
9	B O 40	HCDV	0 12	0 16	0 12	0 04	0	0 04	0 25
10	G W 57	ASHD	0 13	0 13	0 13	0	0	0	0 24
11	R S 21	Hyperthyroidism	0 13	0 13	0 11	0	0 02	0 02	0 26
12	C A 29	Hyperthyroidism	0 11	0 11	0 11	0	0	0	0 15
13	B L 28	Mitral insufficiency	0 13	0 14	0 13	0 01	0	0 01	0 26
14	B A 15	RHD	0 14	0 14	0 12	0 02	0	0 02	0 28
15	M E 38	Myocardiopathy CHF	0 10	0 14	0 10	0 04	0	0 04	0 16
16	P F 52	Myocardiopathy CHF mild mitral insufficiency	0 10	0 13	0 10	0 03	0	0 03	0 15
17	T B 50	HCVD	0 17	—	0 15	—	0 02	—	0 30
18	J H 34	HCVD CHF	0 16	0 16	0 16	0	0	0	0 24
19	M E 45	HCVD	0 14	—	0 14	—	0	—	0 28
20	L P 56	ASHD diabetes pulmonary embolism	0 10	0 15	0 10	0 04	0	0 05	0 38

HCVD hypertensive cardiovascular disease

Recording of the atrial and mitral movements does not prolong the phonocardiographic examination by more than five minutes It is probably the most accurate noninvasive method for the timing of the opening of the mitral valve and the opening snap It can be used as a reference tracing in phonocardiography especially in cases where a satisfactory ACG cannot be obtained

The ACG is not exact in timing the opening snap or mitral opening but is accurate in timing the third heart sound In addition to its use as a time reference it can be used for the study of cardiovascular dynamics[11]

Summary

The exact timing of the opening of the mitral valve and of atrial contraction was obtained by utilizing the ultrasonic Doppler

These signals were used as reference points in phonocardiography for the differentiation of the diastolic heart sounds and compared to the ACG utilized for the same purpose in 62 patients

The Doppler signal coincided with the opening snap in all patients with mitral stenosis while the 0 point of the ACG usually followed the opening snap by a time interval of up to 20 msec

The third heart sound bore a very close relationship to the end of the rapid filling wave of the ACG The fourth heart sound was related to the atrial component of the Doppler tracing as well as the A wave of the ACG

Satisfactory Doppler tracings were obtained in all 62 patients while in 11 of these patients a satisfactory ACG could not be obtained

The ultrasonic Doppler method is a noninvasive method that can be used as a reference tracing in phonocardiography especially when a satisfactory ACG cannot be obtained The tracings can be recorded with minimal delay and at no risk or discomfort to the patient The ultrasonic Doppler method is the most reliable and

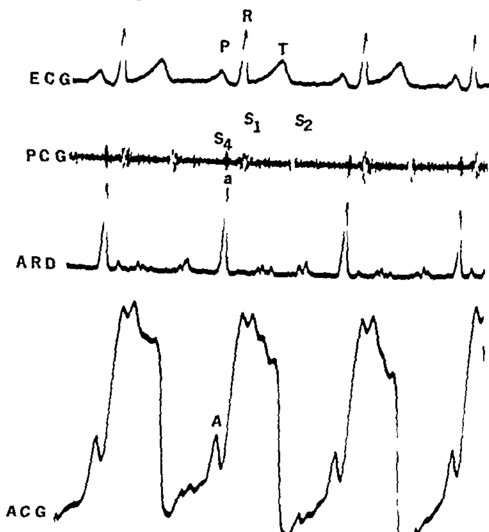


Fig 5 Fourth heart sound (S_4) The S_4 coincides with the atrial wave of the ACG (*A*) and the atrial Doppler signal (*a*)

the opening and closure of the mitral valve more sharply (Figs 1 to 4) and yields tracings that can be recorded easily together with the phonocardiogram and other tracings by many types of recording equipment In addition it is easier to obtain the Doppler tracing than a satisfactory echo and tracings due to the aortic valve can also be obtained

The identification of the third heart sound is easier with the ACG when a satisfactory one is obtained (Fig 3) Since there is no rapid valvular movement during the inscription of the S_3 there is no deflection in the Doppler signal of the mitral valve at that time However a diastolic sound can be diagnosed as an S_3 if it follows the signal due to mitral opening (usually by 20 to 100 msec) and is not an S_4 (Fig 4) The fourth heart sound is identified using the A point of the ACG or the Doppler tracing of the atrial contraction (Fig 5) However in the patients studied the Doppler tracing was more helpful than the ACG because in four of 16 patients a satisfactory ACG could not be obtained and because there was a closer temporal relationship of the S_4 to the A of the Doppler tracing than the A of the ACG The A wave of the ACG was simultaneous with the S_4 in seven of 16 patients while in the remainder it followed the S_4 by 10 to 40 msec This may be due to the delay in transmission of the ACG The A wave of the Doppler tracing coincided with the S_4 in 18 of 25 patients and preceded it in five

The ultrasonic Doppler method is a new noninvasive technique that can be used for the timing of atrial contraction and the opening and closure of the cardiac valves It does not entail any risk of discomfort to the patient and it is not time consuming

able I Mean muscle length cross sectional area and stress at which Max V was measured

Drug	Muscle length (mm ± S D)	Cross sectional area (mm² ± S D)	Stress for Max V (Gm /mm² ± S D)
Lidocaine	5 8 ± 1 6	0 84 ± 0 45	1 2 ± 0 7
Procainamide	4 6 ± 1 1	0 95 ± 0 21	1 4 ± 0 4
Quinidine	5 3 ± 1 2	0 77 ± 0 51	1 4 ± 0 5
Propranolol	6 3 ± 2 3	0 56 ± 0 16	1 7 ± 0 4
Diphenylhydantoin	5 9 ± 0 8	0 64 ± 0 33	1 9 ± 1 3
Bretylium	6 ? ± 1 3	0 54 ± 0 23	1 7 ± 0 6

D = standard deviation.

T03C) with a micrometer until peak ctive tension was at a maximum this ength is L max Twenty minutes for stabilization was then allowed before any measurements were made Peak force and dF/dt development in this preparation were often stable for several hours

Commercially available preparations of each antiarrhythmic drug (propranolol hydrochloride quinidine gluconate sodium diphenylhydantoin lidocaine hydrochloride procainamide hydrochloride and bretylium tosylate) were diluted in Krebs bicarbonate solution such that final bath concentrations of the drug could be achieved by addition of a cumulative volume no greater than 1 to 2 per cent of the volume of the bath After control measurements were made an antiarrhythmic agent was added to the muscle bath to achieve the lowest concentration Fifteen to twenty minutes were allowed to achieve maximal drug effect (stability usually occurred within 5 to 10 minutes after addition of the drug) before a recording was made Sufficient drug was then added to achieve the next concentration and 15 to 20 minutes were allowed for stability before the recording was repeated The preparation was not washed free of drug between each measurement With all drugs except diphenylhydantoin it was sometimes necessary to increase the stimulus following the addition of the drug to maintain contraction Threshold was frequently checked and the stimulus was maintained at 20 per cent above threshold At the end of each experiment the L max of each muscle was measured with a micrometer and the muscle weighed Cross sectional area was [illegible] as uming a cylindrical shape and a specific gravity of 1 0 Six separate papillary muscles were studied for each drug except for diphenylhydantoin where five were studied

Force and dF/dt were tabulated at each hundredth of a second for two consecutive beats Assuming a two component model of muscle mechanics as first described by Hill[1] contractile element velocity (VCE) in muscle lengths per second was digitally computed as VCE = dF/dt/28F where the series elastic constant was taken to be 28[2,3] Stress in Gm per square millimeter was calculated as isometric force in Gm divided by papillary muscle cross sectional area in square millimeters A single stress–velocity curve was plotted from instantaneous VCE and stress calculated from two consecutive beats Max V was recorded as the maximum measured VCE at a low common isometric stress through each experiment (one papillary muscle) V max the contractile element velocity at zero stress was obtained by straight line extrapolation of contractile element velocity to zero stress Peak stress and peak dF/dt were the average of two consecutive beats

The significance of the difference between means of paired variables was determined by the paired Student t test[4] $p < 0.05$ being taken as a statistically significant difference

Results

The mean muscle length mean cross sectional area and average level of isometric stress at which the values of Max V were taken are shown in Table I An example of the effect of a depressant drug lidocaine on the stress–velocity relationship is shown in Fig 1 In this papillary

accurate noninvasive method for the identification of the opening snap and timing of the mitral opening while the ACG is more reliable for the identification of the third heart sound

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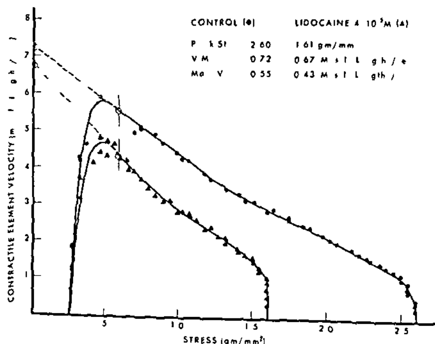


Fig 1 Representative stress velocity curves illustrating depression of contractility by lidocaine (4×10^{-5} M) are shown The *symbol* φ i ustrates the point of common stress at which *Max V* was measured (see text) The straight dashed lines are an extrapolation of the stress–velocity curves to zero stress (V *Max*)

muscle a concentration of lidocaine comparable to that which can be achieved clinically (4×10^{-5} M or 10 mg per liter) resulted in a significant shift in the stress–velocity curve downward and to the left There was depression of both peak stress and Max V *It is interesting to note that* V max obtained by straight line extrapolation was depressed to a lesser degree than the other measures studied *This observation* namely that V max was a less sensitive measure of negative inotropic effect held true for all the drugs with depressant properties (propranolol diphenylhydantoin lidocaine and quinidine)

Fig 2 is an example of an antiarrhythmic agent (bretylium) which augments the stress–velocity relationship The stress–velocity curve is shifted *to the right* and upward resulting in increases in peak stress Max V and V max Note that with positive inotropism V max appeared to more closely reflect changes in contractility as measured by other parameters

Figs 3 to 8 show the dose–response curves for each of the six antiarrhythmic agents studied As previous studies have shown propranolol is a potent myocardial depressant (Fig 3) Statistically significant depression ($p < 0.05$) first occurred in peak dF/dt (to 92 per cent of control) at 10^{-7} M peak *stress (to 84* per cent of control) at 4×10^{-7} M *and in* Max V (to 73 per cent of control) at 10^{-6} M As noted above V *max* was a less sensitive indicator of myocardial depression *with the* first significant depression occurring at 2×10^{-6} M ($p < 0.05$)

Diphenylhydantoin was also a potent *myocardial depressant* (Fig 4) Statistically significant changes ($p < 0.05$) in peak dF/dt *first occurred* at 10^{-5} M (90 per cent of control) in peak stress at 4×10^{-5} M (70 per cent of control) and in Max V at 10^{-4} M (49 per cent of control) The changes *in* V *max* were not statistically significant

In Fig 5 the dose-response curves for lidocaine *showing* depression of all measured parameters of contractility except V *max* are illustrated Statistically significant depression ($p < 0.05$) *in* peak stress first occurred at 2×10^{-5} M (88 per cent of control) *in* peak dF/dt at 4×10^{-5} M (79 per cent of control) and in Max V at 10^{-4} M (69 per cent of control)

The negative inotropic effect of quini

The comparative inotropic effects of six clinically used antiarrhythmic agents

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Most of the antiarrhythmic agents in clinical use have been demonstrated to have some deleterious effect on cardiac function in either man or experimental animals. If the clinical antiarrhythmic properties of some of these agents are similar, then it is of therapeutic significance to know the comparative negative inotropic properties of the agents under consideration at clinically effective blood concentrations. This report compares the effect of six commonly used antiarrhythmic agents, propranolol, quinidine, diphenylhydantoin, lidocaine, procainamide, and bretylium, on the basic stress–velocity relationship of isometrically contracting cat papillary muscle. The effects of each drug were studied over a wide range of concentrations, including levels comparable to blood levels which are achieved clinically.

Methods

Young cats weighing less than one kilogram were killed by cervical fracture and the hearts were quickly removed. A length of 4-0 black silk was tied around the chordae tendineae of a small right ventricular papillary muscle, taking care not to overstretch the muscle, and the muscle was excised. The ventricular end of the papillary muscle was fixed with a metal clip and the tendinous end attached with the silk to a force transducer mounted on a micrometer. The muscle was immersed in a bath of oxygenated Krebs bicarbonate solution maintained at 37° C. and stimulated with a msec. constant current square wave stimulus at a rate of 12 per minute through a pair of punctate electrodes touching the base of the muscle. Isometric force (F) and the first derivative of force (dF/dt) electronically computed with an RC differentiating circuit† were recorded on a direct writing oscillograph.

All experiments were performed at the peak of the length–tension curve. Resting length was increased at 0.1 mm. increments by raising the force transducer (Gras

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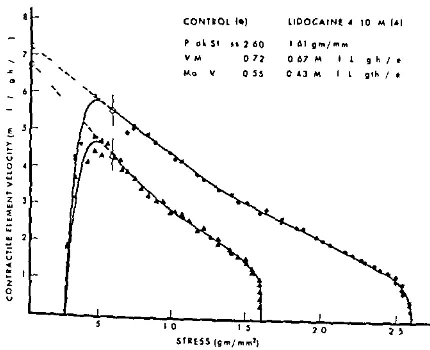


Fig 1 Representative stress–velocity curves illustrating depression of contractility by lidocaine (4×10^{-5} M) are shown The symbol ϕ illustrates the point of common stress at which *Max V* was measured (see text) The straight dashed lines are an extrapolation of the stress–velocity curves to zero stress (V *Max*)

muscle a concentration of lidocaine comparable to that which can be achieved clinically (4×10^{-5} M or 10 mg per liter) resulted in a significant shift in the stress–velocity curve downward and to the left There was depression of both peak stress and Max V It is interesting to note that V max obtained by straight line extrapolation was depressed to a lesser degree than the other measures studied This observation namely that V max was a less sensitive measure of negative inotropic effect held true for all the drugs with depressant properties (propranolol diphenylhydantoin lidocaine and quinidine)

Fig 2 is an example of an antiarrhythmic agent (bretylium) which augments the stress–velocity relationship The stress–velocity curve is shifted to the right and upward resulting in increases in peak stress Max V and V max Note that with positive inotropism V max appeared to more closely reflect changes in contractility as measured by other parameters

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The negative inotropic effect of quini

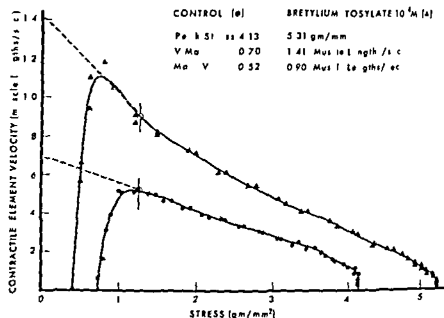


Fig. 2. Representative force-velocity curves illustrating potentiation of contractility by bretylium (10^{-4} M) are shown. The symbol ϕ illustrates the point of common stress at which *Max V* was measured (see text). The straight dashed lines are an extrapolation of the stress-velocity curves to zero stress (*V Max*).

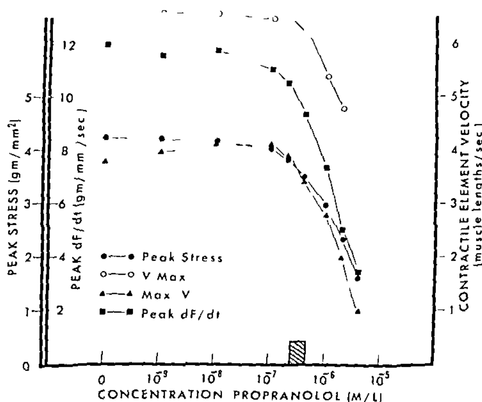
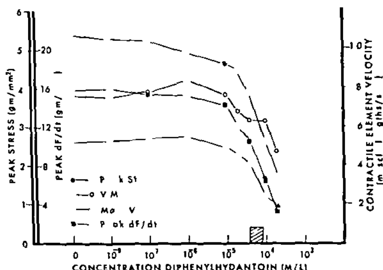


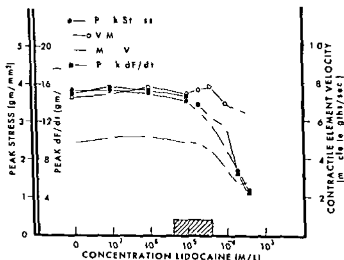
Fig. 3. Average dose-response curves (six papillary muscles) showing the effect of increasing concentration of propranolol. The cross-hatched bar at the bottom represents the range of human therapeutic blood levels.

dine is shown in Fig. 6. Statistically significant depression ($p < 0.05$) in peak dF/dt first occurred at 10^{-5} M (95 per cent of control), in peak stress at 10^{-5} M (95 per cent of control), in Max V at 10^{-4} M (75 per cent of control) and in V max at 4×10^{-4} M (69 per cent of control).

Neither procainamide nor bretylium exhibited any negative inotropic effect but each increased contractility at high doses



F 4 Aver e dose-response curves (five papillary muscles) for diphenylhydantoin The cross hatched bar at the bottom represents the range of human therapeutic blood level



Fi 5 Average dose-re po se urves (s x papillary muscles) for l docaine The crosshatched bar at the bottom represents the range of human therapeutic blood levels

Fig 7 shows the average dose–response curves for procainamide Statistically significant increases ($p < 0.05$) in all four measured parameters occurred at 4×10^{-3} M At this dose peak stress was increased to 123 per cent of control V max to 195 per cent of control Max V to 206 per cent of control and peak dF/dt to 189 per cent of control

With bretylium (Fig 8) statistically significant but very small percentage increases in contractility were seen at very low doses At 10^{-8} M Max V was increased to 109 per cent of control ($p < 0.05$) and peak dF/dt to 106 per cent of control ($p < 0.05$) and at 10^{-7} M peak stress increased to 103 per cent of control ($p < 0.05$) However substantial augmentation of contractility first occurred at about 10^{-4} M where peak stress was increased to 118 per cent of control ($p < 0.05$) V max to 135 per cent of control ($p < 0.05$) Max V to 157 per cent of control and peak dF/dt to 142 per cent of control ($p < 0.05$)

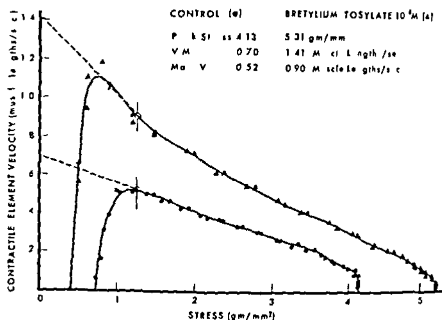


Fig. 2 Representative force-velocity curves illustrating potentiation of contractility by bretylium (10^{-4} M) are shown. The symbol ϕ illustrates the point of common stress at which Max V was measured (see text). The straight dashed lines are an extrapolation of the stress velocity curves to zero stress (V Max).

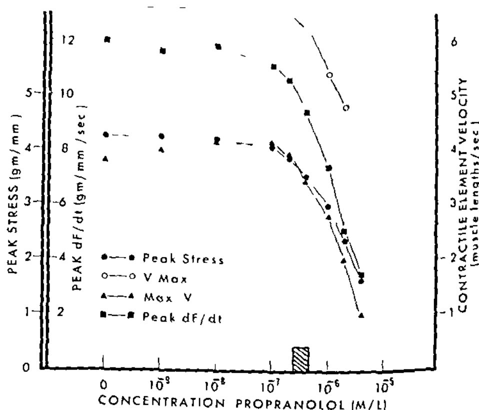
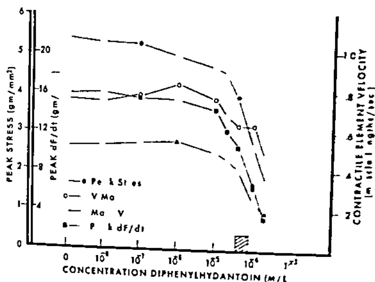


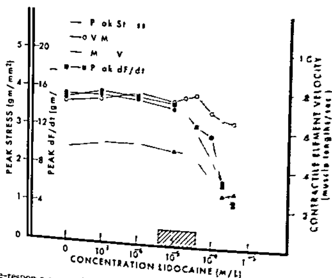
Fig. 3 Average dose-response curves (six papillary muscles) showing the effect of increasing concentrations of propranolol. The cross hatched bar at the bottom represents the range of human therapeutic blood level.

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Neither procainamide nor bretylium exhibited any negative inotropic effect but each increased contractility at high doses



g 4 Average dose-re ponse cu ves (five papillary muscles) for d [illegible] at the bottom represent the ran e of human therapeutic blood levels



5 Avera e dose-response curves (six papillary muscles) f r lid ca e The [illegible] epre ents the ran e of human therapeut c blood levels

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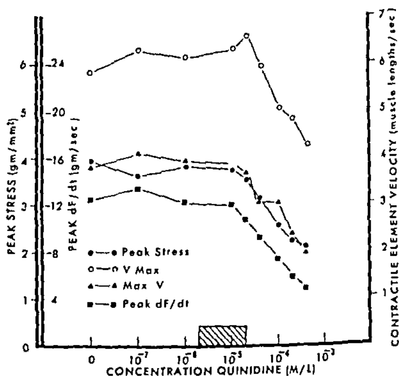


Fig. 6. Average dose-response curves (six papillary muscles) for quinidine. The cross-hatched bar at the bottom represents the range of human therapeutic blood level.

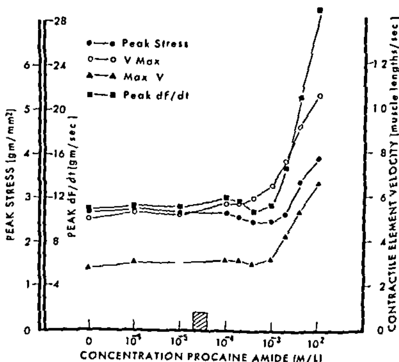


Fig. 7. Average dose-response curves (six papillary muscles) for procainamide. The cross-hatched bar at the bottom represents the range of human therapeutic blood levels.

Discussion

It was the purpose of this study to determine the relative myocardial depressant effects of each of six clinically used antiarrhythmic agents. As shown in the dose response curves in Figs. 3 to 6 propranolol, diphenylhydantoin, lidocaine, and quinidine all decreased the inotropic state of the heart, whereas procainamide and bretylium had no negative inotropic effect at concentrations comparable to human therapeutic blood levels but instead increased

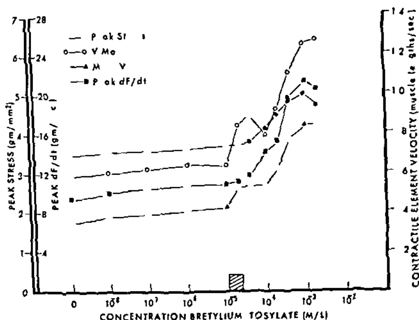


Fig. 8 Average dose-response curves (cat papillary muscle) for bretylium. The cross hatched bar at the bottom represent the range of human therapeutic blood level.

myocardial contractility at very high concentrations. In comparing the inotropic effects of these antiarrhythmic agents it is not necessarily useful in terms of therapeutic information to compare entire dose response curves. Nor is it sufficient to compare each drug at a common molar concentration since the therapeutic blood concentration in man for each drug is different varying over a two hundred fold range from less than 4×10^{-7} M for propranolol to 2×10^{-5} M for diphenylhydantoin (see below). Therefore in ranking each drug according to its myocardial depressant properties the comparison was made at the muscle bath concentration equal to the maximum human therapeutic blood level as previously published in the literature.

Peak plasma propranolol levels following 80 mg oral dose or 10 mg intravenous dose have been recently reported in the range of 100 ng per milliliter (4×10^{-7} M).[5] Plasma levels of diphenylhydantoin of 20 mg per liter (6×10^{-5} M) have been demonstrated to abolish most responsive arrhythmias.[6] In the treatment of ventricular arrhythmias blood levels of lidocaine of up to 10 mg per liter (4×10^{-5} M) have been reported.[7] Oral quinidine given for the conversion of atrial fibrillation to sinus rhythm in doses up to 2.5 Gm per day gave blood levels up to about 10 mg per liter (2×10^{-5} M).[8] The maximum therapeutic blood level for procainamide is about 10 mg per liter (8×10^{-5} M).[9] Few data are available on the human therapeutic blood level of bretylium but it is probably about 16 mg per liter (4×10^{-5} M) or less.[10]

At these maximal therapeutic concentrations each agent was ranked according to decreasing myocardial depressant properties as shown in Table II. Diphenylhydantoin produced statistically significantly more depression ($p < 0.05$) in peak stress and Max V than any other drug. In terms of peak dF/dt diphenylhydantoin was more depressant than quinidine ($p < 0.05$) but not more than lidocaine or propranolol. Lidocaine, propranolol and quinidine did not produce significantly different degrees of depression in peak stress, Max V or peak dF/dt. Lidocaine, propranolol and quinidine all produced significantly ($p < 0.05$) more depression in peak stress, Max V and peak dF/dt than bretylium or procainamide (except in Max V where quinidine was not statistically different from bretylium or procainamide).

As noted above V max was an insensitive measure of contractility and did not sepa

Table II. Per cent of control (control = 100%) for peak stress, V max, Max V, and peak dF/dt at maximum therapeutic concentrations for each of six antiarrhythmic agents

Drug	Maximum therapeutic blood level		Peak stress (% control ± SD)	V max (% control ± SD)	Max V (% control ± SD)	Peak dF/dt (% control ± SD)
	(mg/L)	(M/L)				
Diphenylhydantoin†	20	7×10^{-5}	58 ± 3*	86 ± 30	59 ± 20	67 ± 10
Lidocaine	10	1×10^{-4}	79 ± 16	106 ± 12	90 ± 13	79 ± 18
Propranolol	0.1	4×10^{-7}	81 ± 9	95 ± 14	91 ± 18	78 ± 10
Quinidine	10	2×10^{-5}	88 ± 9*	115 ± 13*	95 ± 15	83 ± 10*
Procainamide	25	1×10^{-4}	101 ± 7	114 ± 25	115 ± 17	108 ± 10
Bretylium	16	4×10^{-5}	106 ± 10	140 ± 63	136 ± 43	117 ± 27

*Values significantly different from control ($p < 0.05$).
†Values for peak stress, V max, Max V, and peak dF/dt are interpolated from actual experimental values.
Abbreviations: SD = standard deviation.

rate any of the drugs at statistically significant levels. This was in part due to the large amount of scatter of the data which may be partly a function of difficulties with extrapolation to zero stress. Max V seems to avoid this problem. Thus considering peak stress, Max V, and peak dF/dt at maximal human therapeutic concentrations, diphenylhydantoin appears to be the most depressant, lidocaine, propranolol and quinidine are about equal; all of these four are more depressant than procainamide and bretylium, both of which produce little change in contractility at these concentrations.

The marked depression of myocardial contractile function by diphenylhydantoin at concentrations comparable to those which are achieved therapeutically in man was somewhat unexpected (Fig. 4 and Table II). However, these results do agree with reports showing some negative inotropic effect of diphenylhydantoin in the intact dog[11] and in patients with heart disease.[12] The suggestion that the negative inotropic effect of diphenylhydantoin may be due to the commercial diluent rather than the drug itself[13] has been disproved by studies in dogs of Mierzwiak, Mitchell, and Shapiro.[11]

An interesting and important finding of this study is that lidocaine, which with less sensitive in vivo techniques is said to have no depressant effect,[14, 16] had a significant negative inotropic effect at concentrations comparable to those achieved clinically. Blood concentrations of lidocaine of 10 mg per liter (4×10^{-5} M), although reported, are probably higher than that routinely achieved and may be in the range causing central nervous system toxicity.[7] A constant infusion of lidocaine at 50 µg per kilogram per minute (3.5 mg per minute in a 70 kilogram man) will produce a blood level of about 5 mg per liter (2×10^{-5} M).[1] At this muscle bath concentration, the depressant effects of lidocaine on papillary muscle were less than those at 4×10^{-5} M (Fig. 5), although peak stress was still significantly reduced to 88 per cent of control ($p < 0.01$).

The previously reported studies on the effects of procainamide on myocardial contractility have shown variable results. In man, procainamide given intravenously causes a decrease in cardiac output[17] and a decrease in right ventricular contractile force.[14] However, O'Rourke and associates[18] could demonstrate no effect of procainamide on the ventricular function curve of the intact conscious dog. The current study demonstrated essentially no effect on myocardial contractility at concentrations comparable to human therapeutic blood level. This suggests that the decrease in cardiac output and right ventricular contractile force observed in some studies may not be due to a decrease in myocardial contractility but to other factors such as a fall in peripheral resistance and/or a fall in ventricular filling pressure. Such has been demonstrated to be the case in studies by

Austen and Moran[19] using dogs with a isolated circulation The reasons for the marked increase in contractility at very high concentrations of procainamide is unknown and is the subject of further investigations

Bretylium has been stated to be a unique antiarrhythmic agent because it is the only antiarrhythmic agent with a positive inotropic effect[20] presumably secondary to catecholamine release[21] The present study demonstrates that within the range of therapeutically achievable concentrations the positive inotropic effect of bretylium was minimal It is only at concentrations five to tenfold higher that a significant potentiation of contractility was noted

This study demonstrated a ranking of decreasing negative inotropic effect for the more commonly used antiarrhythmic agents The data are from cat papillary muscles although the ranking was done at concentrations comparable to human therapeutic concentrations There are several pitfalls in assuming that a similar order of decreasing negative inotropic effect applies to the human clinical situation First there is always the possibility of a significantly different dose–response curve in another species (namely man) Second the model selected (isometrically contracting papillary muscle) may be inappropriate for comparisons with the intact heart Third in contrast to the *in vivo* situation there is no mechanism for excretion or metabolism in another organ such as occurs in the liver with lidocaine

In regard to species difference we have demonstrated a *transient* depressant effect of lidocaine (4 mg per kilogram intravenously) on the intact isovolumically contracting canine left ventricle[22] Other studies using sensitive experimental preparations have demonstrated a similar negative inotropic effect of lidocaine[23] Nayler and associates[4] have shown almost identical dose–response curves to lidocaine for both human and dog papillary muscle preparations Diphenylhydantoin has been previously demonstrated to have at least a transient negative inotropic effect both in the intact canine heart[5] and in man[1] The negative inotropic properties of propranolol[8] and quinidine[27] are well known Of the four drugs demonstrated to have a negative inotropic effect in the cat papillary muscle in this study confirming evidence in other species including man is available for all Thus species differences are unlikely to exist to the extent that the results of this study are not applicable to the human therapeutic situation An important finding of this study is that lidocaine and diphenylhydantoin two antiarrhythmic agents not widely known for their myocardial depressant properties have a significant negative inotropic effect comparable to or greater than that of quinidine

Transference of data obtained in a relatively simple system such as the isometrically contracting papillary muscle to the more complex auxotonically beating intact heart may present some problems The fact that lidocaine produces depression in the papillary muscle but not in the intact heart[15,16] suggests that the papillary muscle preparation is more sensitive to a negative inotropic stimulus However it is conceivable that conditions exist in the papillary muscle (such as cellular hypoxia) so as to result in a significant depressant effect from an agent that would have little effect on the intact heart

Finally there is of course no mechanism for excretion or non cardiac metabolism in this system In the intact animal lidocaine given as a single bolus has *only a transient* myocardial depressant effect lasting about ten minutes[22] This of course is due to its rapid metabolism in the liver However with many antiarrhythmic agents and especially lidocaine the desire is to maintain a near constant blood level often by continuous intravenous infusion Thus in this regard the papillary muscle preparation is analogous as presumably the concentrations of the drug in the bath change very little

Summary

The comparative inotropic effect of propranolol diphenylhydantoin lidocaine quinidine procainamide and bretylium on myocardial contractility was studied using the force–velocity relationship of isometrically contracting cat papillary muscles Dose–response curves over a wide concentration range were obtained Propranolol diphenylhydantoin lidocaine and quinidine all produced significant myocardial

Table II Per cent of control (control = 100%) for peak stress, V max, Max V and peak dF/dt at maximum therapeutic concentrations for each of six antiarrhythmic agents

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*Values significantly different from control ($p < 0.05$)
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Blood concentrations of lidocaine of 10 mg per liter (4×10^{-5} M), although reported, are probably higher than that routinely achieved and may be in the range causing central nervous system toxicity.[7] A constant infusion of lidocaine at 50 µg per kilogram per minute (3.5 mg per minute for a 70 kilogram man) will produce a blood level of about 5 mg per liter (2×10^{-5} M).[7] At this muscle bath concentration the depressant effects of lidocaine on papillary muscle were less than those at 4×10^{-5} M (Fig. 5), although peak stress was still significantly reduced to 88 per cent of control ($p < 0.01$).

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The electrocardiographic effects of elevated cerebrospinal fluid pressure Wolff-Parkinson-White type of conduction disturbance

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Excessive sympathetic stimulation and catecholamine release with intracranial lesions injuries and subarachnoid hemorrhage may produce electrocardiographic changes and myocardial degeneration [1,2] This has been well summarized in a recent editorial by Burch Colcolough and Giles [3] Electrical stimulation of the brain in animals can produce a Wolff Parkinson White (WPW) type of aberrant conduction [4,5] This is a study of the electrocardiographic effects and production of a WPW type of conduction disturbance in dogs during elevated cerebrospinal fluid (CSF) pressure

Methods

Fourteen mongrel dogs (20 ± 2 kilograms mean ± S D) were anesthetized with pentobarbital 30 mg per kilogram intravenously paralyzed with gallamine triethiodide 2 mg per kilogram intravenously and placed in the left decubitus position An endotracheal tube was inserted and ventilation with periodic hyperinflation was controlled with a constant volume ventilator Ventilation was initially adjusted to maintain end-expired CO_2 at 5 0 to 5 5 per cent and then not changed during the remainder of the study A cardiac catheter was positioned in the ascending aorta for pressure measurements and obtaining arterial blood A seven lead (three limb leads three augmented leads and V_4 recorded at the point of maximal cardiac impulse) electrocardiogram (ECG) was recorded Serum sodium and potassium were done with an Instrumentation Laboratory Flame Photometer model 147 Serum glucose was done using a *modified* ferricyanide reduction method[6] on a Technicon autoanalyzer

The technique for elevating cerebrospinal fluid pressure has been previously described in detail [7] Briefly an 18 gauge needle was percutaneously placed into the cisterna magna and connected to a pressure transducer and a pressure reservoir of saline solution (37 C) buffered with sodium bicarbonate to pH 7 4 After control ECG aortic pressure arterial blood gas tensions glucose potassium and sodium values were obtained the CSF pressure was increased over a period of one minute to 100 mm Hg and maintained for 10 minutes An ECG and aortic pressure were recorded after

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depressant effects at concentrations comparable to human therapeutic blood levels. At these concentrations procainamide and bretylium tosylate had little effect on contractility, but both had a marked inotropic effect at very high concentrations. When compared at concentrations comparable to the maximal human therapeutic concentration, the following order of decreasing negative inotropic effect was observed: diphenylhydantoin > lidocaine = propranolol = quinidine > procainamide = bretylium. This study emphasizes the negative inotropic potential of lidocaine and diphenylhydantoin, two drugs not commonly considered to be myocardial depressant agents.

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The electrocardiographic effects of elevated cerebrospinal fluid pressure Wolff-Parkinson-White type of conduction disturbance

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Excessive sympathetic stimulation and catecholamine release with intracranial lesions, injuries, and subarachnoid hemorrhage may produce electrocardiographic changes and myocardial degeneration.[1] This has been well summarized in a recent editorial by Burch, Colcolough, and Giles.[2] Electrical stimulation of the brain in animals can produce a Wolff-Parkinson-White (WPW) type of aberrant conduction.[4] This is a study of the electrocardiographic effects and production of a WPW type of conduction disturbance in dogs during elevated cerebrospinal fluid (CSF) pressure.

Methods

Fourteen mongrel dogs (20 ± 2 kilograms, mean ± S.D.) were anesthetized with pentobarbital, 30 mg. per kilogram intravenously, paralyzed with gallamine triethiodide, 2 mg. per kilogram intravenously, and placed in the left decubitus position. An endotracheal tube was inserted and ventilation with periodic hyperinflation was controlled with a constant volume ventilator. Ventilation was initially adjusted to maintain end expired CO_2 at 5.0 to 5.5 per cent and then not changed during the remainder of the study. A cardiac catheter was positioned in the ascending aorta for pressure measurements and obtaining arterial blood. A seven lead (three limb leads, three augmented leads, and V_4 recorded at the point of maximal cardiac impulse) electrocardiogram (ECG) was recorded. Serum sodium and potassium were done with an Instrumentation Laboratory Flame Photometer, model 147. Serum glucose was done using a modified ferricyanide reduction method[6] on a Technicon autoanalyzer.

The technique for elevating cerebrospinal fluid pressure has been previously described in detail.[7] Briefly, an 18 gauge needle was percutaneously placed into the cisterna magna and connected to a pressure transducer and a pressure reservoir of saline solution (37° C.) buffered with sodium bicarbonate to pH 7.4. After control ECG, aortic pressure, arterial blood gas tensions, glucose, potassium, and sodium values were obtained, the CSF pressure was increased over a period of one minute to 100 mm. Hg and maintained for 10 minutes. An ECG and aortic pressure were recorded after

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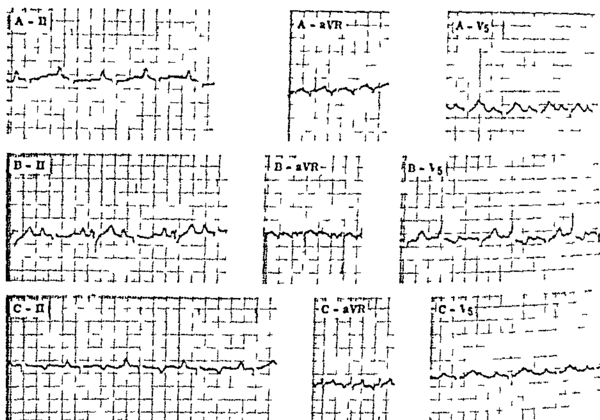


Fig 1 ECG changes during elevated CSF pressure A Control B after CSF pressure elevation to 200 mm Hg for 5 or 10 minutes C 10 minutes after CSF pressure returned to normal Leads II and V_5 recorded at 50 mm per second aV_R recorded at 25 mm per second See text for discussion

5 and 10 minutes of CSF pressure of 100 mm Hg The CSF pressure was then increased to 200 mm Hg for 10 minutes and ECG and aortic pressure were recorded after 5 and 10 minutes of CSF pressure of 200 mm Hg Samples of arterial blood for gas tensions serum potassium sodium and glucose were also obtained after 10 minutes of CSF pressure of 200 mm Hg CSF pressure was returned to normal by permitting fluid to drain from the needle Ten minutes after CSF pressure returned to control level, the ECG and aortic pressure were again recorded and the animals were killed at the conclusion of the study

Significance of change from control values to each experimental period for mean aortic pressure, heart rate and CSF pressure was determined by Dunnett s t test at the 5 per cent and 1 per cent levels [8] Other comparisons were made with the paired t test

Results

Figs 1 and 2 are examples of electrocardiographic changes characteristically evoked by increased CSF pressure In the control state (A) Leads II aV_R and V_5 exhibit a regular sinus rhythm with normal A V conduction and narrow QRS complexes compatible with a vertical or semivertical axis in the frontal plane Following elevation of the CSF pressure to 200 mm Hg for 5 or 10 minutes (B) however shortening of the P R segment is observed on alternate complexes The initial portion of the subsequent QRS complex is then slurred forming a delta like wave in Lead V_5 while the terminal maximal QRS vector is oriented superiorly and to the right Secondary T wave changes are then inscribed No change was observed in the P-S interval despite the P R shortening and QRS prolongation Ten minutes after restoration of CSF pressure to normal (C) the P R interval and QRS configuration following each sinoatrial complex resumes the control configuration and axis orientation

Figs 3 and 4 are additional examples of electrocardiographic changes evoked by elevation of CSF pressure Leads II aV_R and V_5 are again shown in the control state (A), following CSF pressure elevation (B)

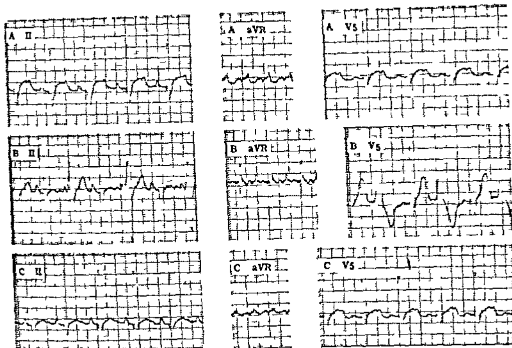


Fig 2 Same legend as Fig 1 see text for discussion

and after recovery (*C*) Elevation of the CSF pressure is associated with aberrant ventricular conduction of sinoatrial impulses following alternate P waves The pattern of abnormal conduction was quite similar demonstrating left axis deviation and terminal forces directed to the right while the QRS complexes were initiated in V₁ by upright delta like waves Following recovery the tracings reverted to normal

Fig 2 demonstrates three separate examples of phasic variation in the extent of the alteration in ventricular activation using Lead II An example of the latter is illustrated in study *A* After a normal control (left) aberrant conduction was observed quadrigeminally and to a variable degree with elevated CSF pressure (right) Moreover the more marked aberration followed the more abbreviated P R segment The timing of the aberrantly conducted ventricular complexes did not conform to a parasystolic focus In study *B* CSF pressure elevation (right) is associated with a sinoatrial conduction that is succeeded uniformly by aberrant conduction Alternate P waves in this example are succeeded by marked left axis deviation following a very short and fixed P R interval The intervening P waves are succeeded by a P R of variable duration and the degree of aberrance (i e left axis deviation) varies inversely with the duration of the antecedent P R interval Study *C* provides further illustration that phasic variation in QRS configuration and P R intervals is associated with the disordered ventricular activation Following the control tracing (left) CSF pressure elevation (right) evoked aberrant ventricular conduction with P R shortening in alternate complexes A phasic variation is also exhibited in the QRS configuration The QRS complex becomes progressively less aberrant in this tracing over an interval enclosing five complexes with anomalous conduction The P R interval also appears shortest preceding the QRS with the most marked left axis deviation A parasystolic focus could not explain what might otherwise be construed as variable degrees of ventricular fusion

Of the 14 animals studied 10 exhibited electrocardiographic changes of a distinctive nature These changes were moreover quite similar with regard to both the pattern of change and the temporal sequence of their occurrence When the CSF pressure was elevated to 200 mm Hg for either 5 or

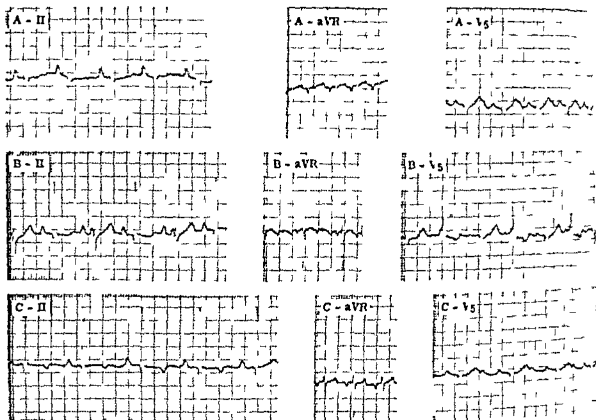


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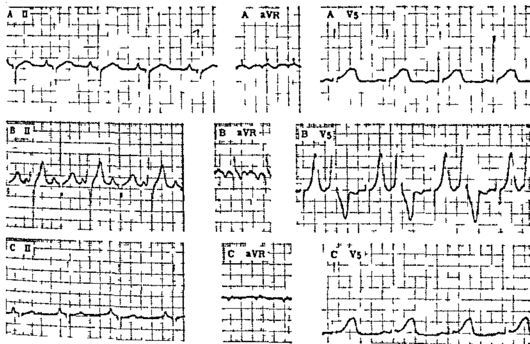


Fig 4 Same legend as Fig 1 see text for discussion

ivity Stimulation of certain areas of the posterior hypothalamus elicited alternate P R shortening and QRS prolongation which closely resembled the WPW phenomenon Parker Gunn and Lynn[5] observed aberrant electrocardiographic complexes resembling the WPW structure following electrical stimulation of both the posterior hypothalamus and the midline reticular formation in cats Finally Mauck Hockman and Hoff[9] produced P R abbreviation QRS prolongation and delta waves in alternate ECG complexes by electrical stimulation of the mesencephalic reticular formation at the level of the pons in dogs Similar to the present study the *alternate* complexes demonstrated phasic variation in the degree of aberration with increasing P R attenuation that was succeeded by the elaboration of an increasingly more marked aberration of the QRS complex

The nature of this peculiar cardiac response to cerebral stimulation has not been elucidated but a variety of theories have been proposed The interaction of vagal and sympathetic influences in the production of cardiac arrhythmias after electrical stimulation of the diencephalon in cats was described by Manning and Cotten[10] Weinberg and Fuster[4] have suggested that the alteration in atrioventricular conduction after electrical hypothalamic stimulation may be the consequence of delayed reflex activation of cardioregulatory centers in the nervous system Other investigators have suggested that the electrocardiographic changes were the consequence of reflex vagal discharge[5] In contrast Mauck Hockman and Hoff[9] demonstrated that vagal stimulation suppressed abnormal ventricular activation and concluded that the WPW like electrocardiographic phenomenon was mediated exclusively by the sympathetic division of the autonomic nervous system Gallamine triethiodide which has a significant sympathomimetic and atropine like action on the heart[11] was used in the present study for skeletal muscle paralysis Vagal effects on the heart in these animals were probably not significant

Previous studies from this laboratory[7,12] using an identical animal model have suggested that a large and distinct adrenergic stimulus occurs when CSF pressure is elevated to 200 mm Hg No change in plasma norepinephrine was found during elevated CSF pressure but this does not exclude changes in catecholamines that may be physiologically significant[13] Additional evi

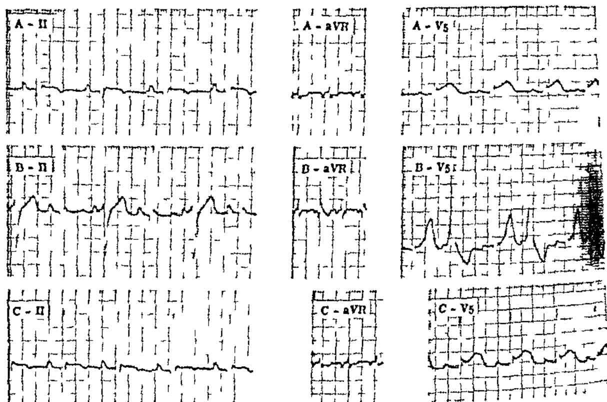


Fig. 3. Same legend as Fig. 1. See text for discussion.

10 minutes shortening of the P R interval was observed in alternate electrocardiographic complexes while the associated QRS complexes were widened with marked left axis deviation and terminal forces directed to the right as in Figs. 1 to 4. With continued CSF pressure elevation the pattern of P R shortening and QRS prolongation typically became more persistent and in seven of the animals exhibited phasic changes in the ECG as in Fig. 5. This phasic change consisted of progressive P R abbreviation with proportionate widening and aberration of the associated QRS complex such that little or no alteration of the total P S interval took place. In only one experiment was A V dissociation observed following an earlier sequence of a typical bigeminal response. Evidence for a parasystolic focus of ectopic activity was discerned in none of the experiments. Thus in each case the abnormal ventricular activation succeeded and, as a consequence, appeared dependent upon the antecedent sinoatrial impulse. Moreover, a typical upright delta-like wave initiated the aberrant QRS complex in one or more ECG leads. This was observed uniformly in Lead V_5 and occasionally in Leads II and III (Figs. 1 to 4). The ECG returned to normal in all 10 dogs after the CSF pressure was returned t control levels for 10 minutes.

Table I demonstrates the mean aort pressure, arterial gas tensions and plas sodium, potassium and glucose. The aort pressure increased significantly when CS pressure was increased from 100 to 7 mm Hg. Serum potassium showed a sta tistically significant decrease and seru glucose increased.

Discussion

This study provides evidence that el vation of the CSF pressure evokes an alte tion in the pattern of ventricular activati that is at least superficially similar to t exhibited in the WPW syndrome. The el trocardiographic data strongly suggest th the altered QRS complexes reflect an ano alous pattern of ventricular activati rather than ectopic ventricular comple exhibiting a varying degree of fusion w the sinoventricular complexes.

Other investigators have observed a re tion between cerebral stimulation and c diac rhythm. Weinberg and Fuster[4] u electrical stimulation of the lateral posterior hypothalamus in the cat to p duce ECG manifestations of ectopic v tricular and/or junctional pacemaker

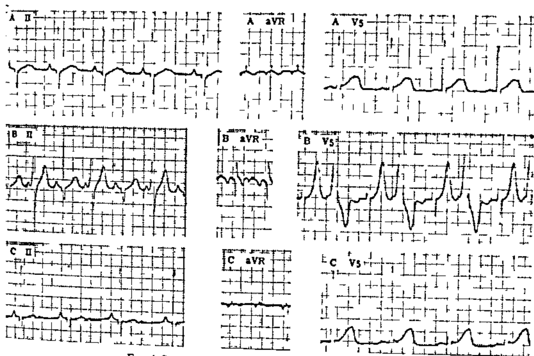


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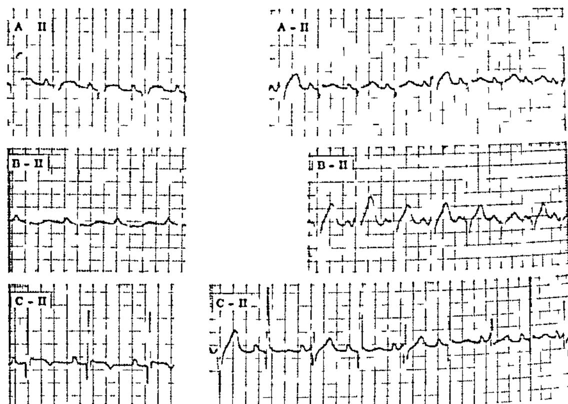


Fig. 5. Three separate examples (*A*, *B*, *C*) of phasic variation in the alteration of ventricular action. Control tracing left and tracing after elevation of CSF pressure to 200 mm. Hg for 5 or 10 minutes on right. Paper speed was 50 mm. per second. See text for discussion.

dence of sympathetic stimulation is demonstrated by the increase in plasma glucose.[14] Intravenously administered catecholamines and cardiac sympathetic nerve stimulation enhance conduction through the A-V node.[15, 16] WPW may be related to catecholamines or sympathetic stimulation since it has been suggested that WPW aberration may result from a failure of part of the A-V node to delay the impulse normally in its passage through the node.[17]

Elevated CSF pressure, by direct stimulation of the brain or by producing cerebral ischemia, can produce a WPW type of aberrant conduction. The data described in these experiments certainly suggest that WPW-like anomalous conduction may result from neurohumoral factors and need not be contingent upon anatomically discrete anomalous pathways. This aberrant conduction probably represents a significant but reversible sympathetic discharge, either neurogenic, humoral, or both.

Summary

Cerebrospinal fluid pressure was elevated in 14 dogs and an ECG was recorded before elevation of CSF pressure, 5 and 10 minutes after CSF pressure elevation to 100 mm. Hg, 5 and 10 minutes after CSF pressure elevation to 200 mm. Hg, and 10 minutes after CSF pressure returned to control levels. In 10 of the 14 studies the ECG exhibited what appeared to be anomalous A-V conduction with a short P-R and widened QRS. This usually occurred in alternate complexes but occasionally a phasic cyclical pattern was observed with progressive shortening of P-R and widening of QRS. With the short P-R the QRS consistently assumed a left axis deviation with rightward directed terminal forces and distinct delta waves were inscribed in the anomalous left precordial complexes. Systemic blood pressure, heart rate, and serum glucose were significantly elevated during CSF pressure of 200 mm. Hg. These data suggest that WPW-like anomalous conduction may result from neurohumoral factors and need not be dependent on abnormal anatomical pathways.

The authors express gratitude to Dr. Pao-lu Yu for statistics and Miss Cherry N. Smith and Mr. R. L. De Atley for technical assistance. Compu

Table I Effects of elevated CSF pressure in 14 dogs

	CSF pressure					
	Control	5 min 100 mm Hg	10 min 100 mm Hg	5 min 200 mm Hg	10 min 200 mm Hg	10 min control
Aorta mean (mm Hg)	1?7 ± 16	131 ± 11	134 ± 10	195 ± 10	188 ± 35	129 ± 1?
Heart rate (per minute)	163 ± ?7	1 5 ± 72	164 ± 25	191 ± 30†	?0? ± 34†	143 ± ?4
CSF (mm Hg)	4 ± 1	99 ± ?	99 ± 3	201 ± 3	00 ± 3	5 ± 1
Arterial pH	7 4? ± 0 03				7 34 ± 0 04	
Arterial P_{CO_2} (mm. H)	3, ± ?				40 ± ?	
Arterial P_{O_2} (mm Hg)	87 ± 6				81 ± 8	
Hematocrit (per cent)	38 ± 7				46 ± 7	
Potassium (mEq /L)	4 0 ± 0 4				3 6 ± 0 3	
Sodium (mEq /L)	143 ± 2				144 ± 2†	
Glucose (m per cent)	94 ± 15				136 ± 3?	

\al re me ± ta d d d ıat (S D) S g ificance f hange f om co trol period P < 0 01 †P < 0 05

tat ons were performed at Indiana University Medical Center computer facility supported in part by Public Health Service Research Grant RR 0016?

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The sequence of normal ventricular recovery

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The sequence of ventricular repolarization has been defined in less detail than ventricular activation order. Activation sequence has been mapped by timing QRS spikes in electrograms from closely spaced bipolar electrodes. These data have been used to explain QRS waveform in normal and some abnormal states, and the diagnostic utility of the ECG has been improved by the insights provided by these studies. Because of its longer time course and greater lability, ventricular recovery sequence is more difficult to define than activation order. In vivo transmembrane action potentials have been successfully recorded only from the epicardial surface of the ventricles and suction electrode potentials have been recorded from only a limited number of sites. To date, these methods have not been used for a systematic study of recovery properties. There is reasonably good evidence that functional refractory periods (FRP's) reflect action potential duration of ventricular muscle[1] and this is the most frequently employed method of assessing recovery properties. van Dam and Durrer[2] determined the intramural distribution of refractory periods at a single location in the mid anterolateral portion of the left ventricle. They reported an endocardial to epicardial gradient with endocardial refractory periods being longer than those in intramural and epicardial layers. The present study reports the distribution of refractory periods at multiple epicardial sites, their intramural distribution at the apex and base of the left ventricle, and their distribution in the interventricular septum. In addition to the previously reported endocardial to epicardial gradient of refractory periods in the left ventricle, an apex to base gradient was found with left ventricular apical FRP's being longer than those at the base. FRP's in the apex of the interventricular septum were also longer than those at the base, and FRP's on the left side of the septum were longer than those on the right side of the septum.

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Methods

Studies were done on 23 dogs anesthetized with pentobarbital 30 mg per kilogram of body weight. The chest was opened with a sternal splitting incision and respiration was maintained with a fixed volume pump respirator. The heart was suspended in a pericardial cradle and a bipolar electrode attached to the right atrial appendage. The sinus node was crushed and the atria paced with a basic drive (S_1) at a cycle length of 400 msec. In some experiments pairs of fine nichrome wires 0.0025 inch in diameter were sewn at 3 to 8 epicardial sites. The wires were insulated except for the portion embedded in the epicardium. In other experiments a multielectrode needle was placed in the wall of the ventricle at the base or apex. The multielectrode needle had 7 pairs of 0.1 mm diameter electrodes spaced along 11 mm of the needle shaft. The pairs of electrodes were 0.6 mm apart and there was 0.1 mm between poles of electrode pairs. In these animals the chest was closed with wound clips and the animal placed on a DC powered heating pad. The animals were permitted to stabilize for a minimum of 10 minutes before measurements were made. To measure septal FRP's electrodes were specially constructed from strands of the 0.0025 inch diameter nichrome wire. Two strands of wire were spun in a spiral and one end of the spiral was embedded in a plug of epoxy glue. The insulation was scraped from adjacent turns of the spiral to produce a closely spaced bipolar electrode. To place the electrodes they were first threaded onto a long "darning" needle. The free wall of the left ventricle was then cannulated with an 18 gauge needle and the "darning" needle was passed through it, the septum, and the free wall of the right ventricle. The epoxy plug anchored the electrode against the septum. For some experiments the insulation was scraped 5 mm from the epoxy plug. In other experiments three spirals were embedded in the epoxy plug and the insulation on respective strands was scraped at 2, 4, and 8 mm distances from the plug. This resulted in electrodes on the left endocardial surface of the septum, the middle layer of the septum, and on the right endocardial surface of the septum. At the end of the experiments the hearts were dissected and the positions of the electrodes were documented. The dissected heart of one dog with the septal electrodes in place is shown in Fig. 1A and a photograph of a three spiral electrode and the needles used for placing it are shown in Fig. 1B.

As a step in assessing FRP's, activation times at the test sites were determined. A light beam oscillograph was used to record electrograms from each pair of bipolar electrodes at a paper speed of 2,000 mm per second. The frequency response of the recording system was flat within ±5 per cent to 600 Hz. An example of the recordings is shown in Fig. 2. S_1 was displayed on one channel and activation time at the test sites was measured from S_1 to the peak of the largest sharp deflection recorded in the bipolar electrograms. Test stimuli (S_2) were twice threshold cathodal "make" stimuli delivered to one pole of the pairs of electrodes. S_2 was a rectangular pulse of long duration so placed that the "make" was in the early part of the T wave and the "break" was within the next QRS complex. With this placement the pulse did not produce a ventricular response. The onset of the test pulse was then delayed with respect to S_1 in 1 msec increments until a propagated ventricular response resulted. The test pulse was displayed on an oscilloscope along with an epicardial electrogram used to detect propagated responses and to determine that they were secondary to the cathodal "make" portion of the test pulse. In some animals one or more of the test sites responded during the plateau of the test pulse rather than on the "make" and measurements from these test sites were discarded. Responses in the plateaus of long duration pulses have also been observed by Dekker.[3] At least one minute was permitted to pass between each measurement to decrease the effect of preceding short cycle lengths on the FRP.[4,5] In each experiment some test sites were kept as reference points and measurements were frequently repeated at these sites. If FRP's at these sites varied by more than 5 msec the preparation was considered to be unstable and the measurements discarded.

In four experiments only epicardial FRP's were measured. In these animals one

The sequence of normal ventricular recovery

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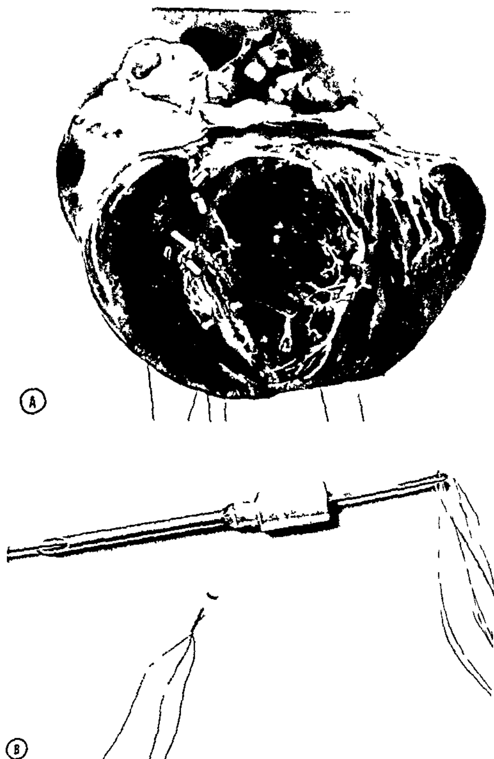


Fig. 1 A and B Photograph of a dog heart is shown in panel *A*. The left ventricle has been opened to expose the septum. The epoxy glue plugs which anchored the spiral electrodes in the septum are seen. Two electrodes are at the base of the septum, two in the midportion of the septum, and two at the apex. The epoxy plug end of a three spiral electrode and the needles used for placing the electrodes are shown in panel *B*.

or two pairs of electrodes were placed at the posterior base of the left ventricle, the apex of the right and left ventricles, the base of the lateral wall of the right and left ventricles, and the mid anterior portion of the right ventricle. In four additional experiments transmural FRP's were measured in addition to epicardial FRP's. In two of these experiments only a limited number of epicardial test sites were used as reference points. Two sites were tested in one of these experiments and three in the other.

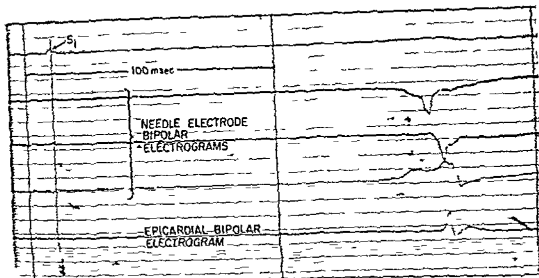


Fig 2 Electrograms used to determine activation order Closely spaced bipolar electrodes were used and recordings taken on a light beam oscillograph at a paper speed of 2 000 mm per second The basic atrial driving stimulus (S1) is displayed on the first channel Electrograms from the multielectrode needle are displayed on the second third and fourth channel and an electrogram from a pair of electrodes sutured to the epicardial surface is displayed on the fifth channel

In 11 dogs the FRP s in only the middle layer of the base mid portion and apex of the interventricular septum were measured with 1 to 3 electrodes positioned in each location In 4 additional dogs FRP s were measured on the left ventricular endocardial surface the middle layer and the right ventricular endocardial surface of the base and apex of the septum One or two electrodes were positioned in each location

Results

Epicardial FRP s In seven experiments in which epicardial electrodes were placed on the base and apex of the left ventricle apical FRP s were 5 to 20 msec longer than those at the base A graph showing the comparison of average apical to average basal FRP s in individual experiments is shown in Fig 3 In some experiments FRP s at individual sites on the apex and base of the left ventricle overlapped but the average values at the apex were longer than those at the base in all experiments There were six experiments in which there were two or more test sites at both the base and the apex of the left ventricle The graphs in Fig 4 show the FRP values at individual apical and basal test sites

Fewer test sites were placed on the right than on the left ventricle In four of six experiments in which electrodes were placed on the apex and base of the right ventricle one or the other of the sites had to be discarded because the test stimulus produced a response on the plateau rather than on the make In the other two experiments the FRP at the apex was 12 msec longer than that at the base in one experiment and 14 msec longer in the other

There was no systematic relationship of FRP s in the free wall of the right ventricle in comparison to those in the free wall of the left ventricle In three experiments the averages of right ventricular FRP s were shorter than those of left ventricular FRP s In two experiments average right and left ventricular FRP s were equal and in one experiment average right ventricular FRP s were longer than those in the left ventricle

Intramural FRP s The intramural distribution of FRP s was assessed in 4 dogs The multielectrode needle was placed in the posterior base of the left ventricle in one animal in the lateral wall of the left ventricle near the apex in two animals and in both of these locations in one animal The results of the experiments in these 4 dogs are shown in Fig 5 The solid lines indicate the measurements from the posterior base of the left ventricle and the broken lines indicate a left lateral site near

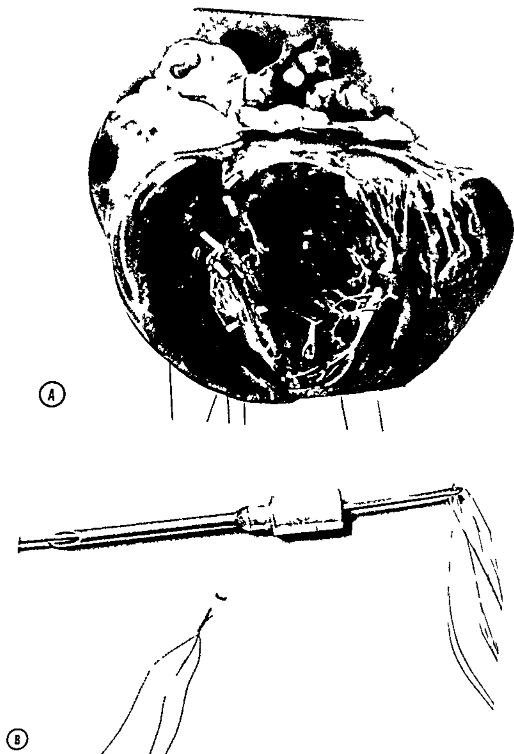


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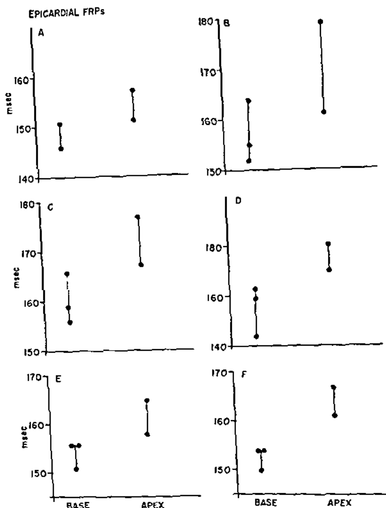


Fig 4 Graphs from data of 6 experiments showing the disparity of FRPs at left ventricular basal and apical sites and the relationship between these. Each point represents a separate test site. In part *B* the FRP from one basal test site was longer than the FRP from one apical test site and in part *A* the FRP from one basal and one apical test site were equal. However in each experiment averages of FRPs from all basal sites were always shorter than averages of FRPs from all apical sites.

other instances shorter than the FRPs on the right side of the septum. In the animal illustrated in D (Fig 6) the average FRP in the middle layer of the septum at the base was longer than the average FRP in the middle layer of the septum at the apex. In all other instances apical FRPs were longer than basal FRPs at comparable interventricular sites.

Discussion

In 1934 Wilson and colleagues[8] noted that if recovery properties of the ventricle were uniform the QRS and T waves would be equal in area and opposite in polarity. That is, the QRST area or ventricular gradient would be zero. They further suggested that the degree to which the QRST area deviated from zero was a measure of the non uniformity of recovery properties. Attempts to define the distribution of ventricular recovery properties have been complicated by the extreme lability of that process. Changes in heart rate, temperature, depth of anesthesia, sympathetic tone and electrolyte balance all influence recovery properties. In addition, unlike ventricular activation time which can be defined precisely, there is no electrogram deflection that clearly marks the onset or termination

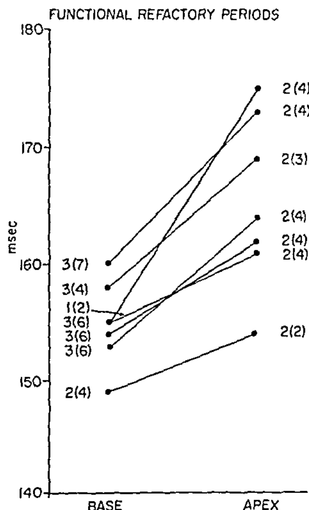


Fig 3 Graph of the relationship of left ventricular basal to apical FRP in seven experiments The values shown are average The numbers indicate the number of sites tested and the number of measurements made For example *3 (7)* indicates an average of 7 measurements was taken at 3 test site In all instances basal FRP's are shorter than apical FRP's

the apex The stars indicate FRP's at an epicardial reference test site The epicardial measurements were made before and after measurements of intramural FRP's and are an indication of the stability of the preparation Endocardial FRP's were longer than epicardial FRP's in all experiments FRP's were progressively shorter from the endocardium to the epicardium in all but one experiment In the experiment illustrated in Fig 5 "D," the deepest endocardial test site had an FRP 14 msec shorter than the next test site, but FRP's at both of these sites were longer than the epicardial FRP in this location These results correspond to van Dam and Durrer's[2] finding of longer endocardial than epicardial refractory periods However van Dam and Durrer's finding that the shortest FRP's were located in the middle layers of the ventricle was not documented in this study

Septal FRP's In 11 dogs the refractory periods were measured at 1 to 3 sites in the base and apex of the interventricular septum at positions midway between the right and left ventricular cavities In 7 of these animals FRP's were also measured at 1 to 2 sites at a level between the apex and base In 10 of the experiments apical FRP's were from 2 to 21 msec longer than those at the base In the remaining experiment the basal FRP's were 3 msec longer than those at the apex In the animals in which FRP's were measured at a level midway between the apex and base the FRP's at this level were 2 to 10 msec longer than basal FRP's in 6 dogs and 4 msec shorter than basal FRP's in the other dog

In four additional dogs the distribution of FRP's across the thickness of the apex and base of the septum was studied The results from these 4 dogs are shown in the graphs in Fig 6 The graphs on the left show the averages of the FRP's at apex and base on the right side of the septum in comparison to the average of the FRP at apex and base on the left side of th septum The graphs on the right show FRP's on the right side of the septum middle layer of the septum and left of the septum at the base (solid lines) comparison to the apex (broken lines) shown on the left side of the figure in four animals the average of FRP's on th right side of the septum was less than th average of FRP's of the left side of th septum For the individual animals FRP on the right side of the septum average 2 11 1 and 6 msec less than the FRP's the left side of the septum On the right the figure the relation of apical to basal se tal FRP's on the right side of the septu left side of the septum and a site midw between these two locations is illustrate Average FRP's on the right side of th septum are shorter than average FRP's the left side of the septum and those at th base of the septum are shorter than tho at the apex The FRP's at the sites midw between the right and left sides of the se tum are in some instances longer and

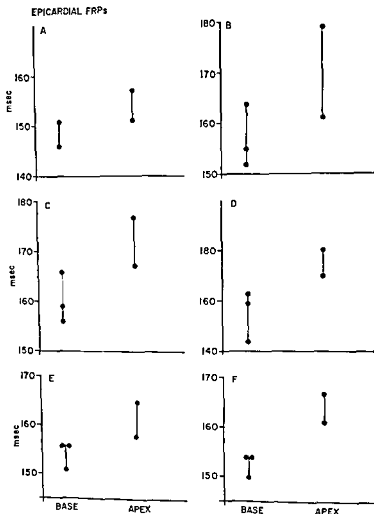


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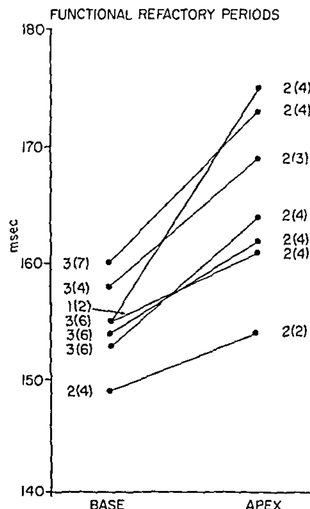


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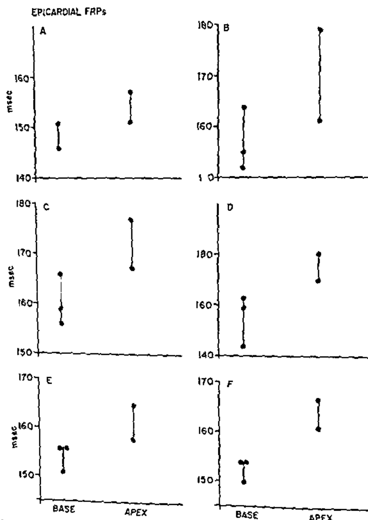


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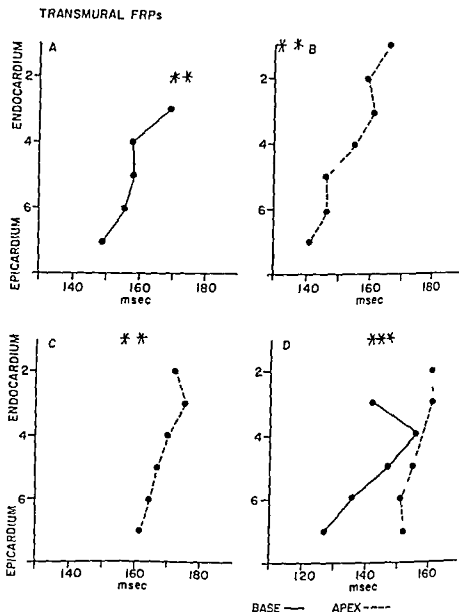


Fig 5 Graphs of the intramural distribution of FRP's in 4 experiments The electrode sites are indicated on the ordinate and the duration of FRP's in msec is plotted on the abscissa The solid lines indicate measurements from the base of the left ventricle and the broken lines indicate measurements from the apex The stars represent FRP's at epicardial reference test sites These measurements were taken before and after the intramural measurements were completed and are an indication of the stability of the preparation

of the recovery process under a test electrode Pipberger and co workers[7] attempted to define the distribution of ventricular recovery properties in dogs by comparing the time of the peak amplitude of T waves at multiple ventricular sites They concluded that recovery time at the base of the ventricle was shorter than that at the apex Haas[8] in a study utilizing local leads also concluded that there was a base to apex gradient of recovery properties but stated that basal recovery times were longer than those at the apex Both of these studies were qualitative and the degree to which recovery properties in the ventricles varied was not assessed

In the present study functional refractory periods were used to assess the base to apex as well as the endocardial to epicardial distribution of recovery properties in the free walls and septum of the ventricles Several precautions were taken to assure the stability of the preparation and the accuracy of the measurements Heart rate was kept constant One or more test sites were repeatedly checked during the course of the experiments to evaluate the stability of the measurements Difference

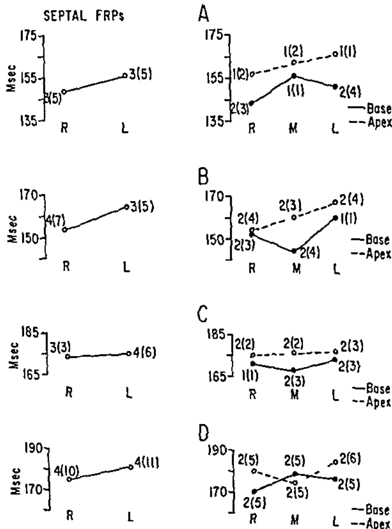


Fig 6 Graph of the relationship of right to-left and base to-apex septal FRP s of 4 dogs The data points represent averages A in Fig 3 the numbers next to the data points indicate the number of test sites and the number of measurements included in the average R L and M refer to the location of test sites R = right endocardial surface of the septum L = left endocardial surface of the septum and M = a position midway between these two locations The graph on the left of the figure show that FRP s on the right side of the interventricular septum were shorter than those on the left The graphs at the right of the figure show the relationship of apical (broken line) to basal (solid line) FRP s FRP at the base of the septum are shorter than those at the apex

in threshold to cathodal make and break and anodal make and break stimuli have been defined and can influence refractory period measurements[3] Therefore all test stimuli in this study were cathodal make at two times diastolic threshold To decrease the effect of varying preceding cycle length on refractory period measurement[4 5] the onset of the test stimulus was placed in the early part of the T wave and then delayed in 1 msec increments until a response occurred In addition at least 1 minute elapsed after each response to a test stimulus or a spontaneous premature beat before another measurement was made The animals were kept on a DC powered heating pad to help maintain body temperature Activation times were determined at the test sites by recording electrograms from closely spaced bipolar electrodes at a paper speed of 2,000 mm per second Despite these precautions

stable FRP measurements at the reference test sites were not always obtained and such experiments were discarded. The disparity in FRP's found in individual areas of the ventricles in this study was similar to the local disparity of refractory periods observed by Han, Chizzonetti, and Moe.[9]

The failure to find a systematic relationship between FRP's in the right and left ventricles may be due in part to the lesser number of test sites placed on the right ventricle. In addition, right ventricular test sites frequently had to be discarded because they responded on the plateau rather than on the "make" of the test stimulus.

Recovery properties in the free wall of the left ventricle were systematically distributed with long FRP's located in the endocardium and the apex and short FRP's located in the epicardium and the base. Recovery properties in the septum were also systematically distributed with short FRP's located at the base and on the right side of the septum, and long FRP's located at the apex and on the left side of the septum. That is, areas of the ventricle normally activated early had long refractory periods and those areas activated late had short refractory periods. This organization of recovery properties may play a protective role. Disparity in refractory periods is known to be a factor capable of lowering fibrillation threshold.[10] With the arrangement of refractory periods found in this study, recovery would tend to be completed in all portions of the ventricle at almost the same time and the likelihood of re-entrant arrhythmias is decreased.

The data presented are also applicable to understanding T waveform. In a previous report a theoretic model of the T wave was presented.[11] That model was based on the form of the downstroke of the transmembrane action potential and the sequence of activation. Action potential duration was assigned on the basis of van Dam and Durrer's finding of an endocardial to epicardial gradient of FRP's. In addition, it was assumed that all areas of the ventricle activated at the same time had equal action potential duration. Since ventricular activation spreads from apex to base as well as from endocardium to epicardium and predominantly from left side to right side of the interventricular septum, the assignment of action potentials included both an endocardial to epicardial and apex to base gradient of action potential durations in the free wall of the left ventricle and a left to right gradient of action potential durations in the septum. The T waves that were derived with this distribution of recovery properties closely resembled those recorded from dogs.

The data presented in this study are incomplete and only include information concerning refractory period duration. Further studies to define the distribution of FRP's in the right ventricle in comparison to the left ventricle are needed. In addition, data concerning the configuration of the downstroke of the ventricular action potential are required for a more complete understanding of T waveform.

Summary

Functional refractory periods (FRP's) were measured at epicardial, intramural, and septal sites in pentobarbital anesthetized dogs. The sinus node was crushed and the atria were driven at a fixed rate. Activation times at the test sites were measured from electrograms recorded from closely spaced bipolar electrodes. The test stimuli were cathodal "make" stimuli delivered to one pole of the pairs of electrodes. FRP's at the base of the free wall of the left ventricle and of the septum were shorter than FRP's at the apex. FRP's on the epicardium were shorter than those on the endocardium, and FRP's on the right side of the septum were shorter than those on the left side of the septum. The findings indicate that normal ventricular recovery properties are systematically distributed and inversely related to activation sequence. Areas of the ventricle activated early have the longest FRP's, and areas activated late have the shortest FRP's. This distribution of recovery properties tends to make all portions of the ventricles complete recovery at about the same time and may play a protective role in the prevention of re-entrant arrhythmias. This distribution of recovery properties is also applicable to an explanation of the configuration of normal T waves.

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Delayed coronary blood flow detected by computer analysis of serial scans

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Prior to serious complications the diagnosis of ischemic heart disease remains notoriously difficult. The belief exists that if myocardial ischemia can be detected accurately by a reasonably simple and safe test, and when demonstrated can be presumed to be produced by insufficient coronary artery flow, then such a test may be used as an index to the presence of significant ischemic heart disease.[1]

Several authors have reported the use of cesium 131 for myocardial scanning.[2-5] Two problems with its use are known. It is not taken up by muscle as rapidly as potassium or rubidium[6] and its inherent low energy, 29.4 keV x ray, results in some tissue absorption by structures of the chest wall.[7] Photoscans using radioiodinated oleic acid have not proved to be a practical diagnostic method for the detection, location, and estimation of size of myocardial infarcts.[8,9] Dreyfuss and associates[10] have shown increased radioiodine uptake by the total heart after infarction. The technique is time dependent and appears not to be usable with myocardial scanning.[10] Radioiodine albumin macroaggregates (RAMA) have been proposed for coronary artery bed photo scanning.[11] Poe[1] has recently shown that if particle size is too large, a course of events can occur which is similar to that resulting from progressive coronary arterial occlusion. Use of mercury 203 labeled chlormerodrin (Neohydrin) has also been reported.[13,14] This is an isotope which produces a positive area of increased radioisotope concentration at the location of a infarct. The dose required has been too large for human use.

Carr and associates[1] reported the use of rubidium 86 in 1962. Though it has been shown to be a good potassium analog,[4,1] low production of photons prevents its use in humans. Though the high gamma energies of both rubidium 86 and potassium-42 are difficult to collimate, they are not impossible.[16] In 1966 Love and associates[17] reported serial scanning while maintaining a plateau concentration of these isotopes in arterial blood. To show rate of isotope uptake, the application of least square regression analysis to each element in the scanned area has been described.[18,19] The use of three dimensional models hindered

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the realization of the correlation between the values of rate of isotope uptake and zero intercepts

Physically smaller faster and more efficient digital computers and improved displays have become available This report describes the results obtained when this improved equipment processed and displayed the scan data obtained before and after Ameroid* constrictors were placed on selected coronary arteries of dogs [20, 21]

Materials and methods

The isotope scanner in use has been described previously [19] The isotopes potassium 42 and rubidium 86 were chosen because an average of 71 per cent (^{42}K) or 65 per cent (^{86}Rb) is removed by the myocardium during one circulation whereas a lesser amount (22 per cent ^{134}Cs) of the isotopes of cesium are extracted [6]

Three or more sets of scans were made from each of 15 mongrel dogs while they were anesthetized with sodium pentobarbital The first set of scans was made just prior to placing on the artery a 2 77 mm inside diameter uncoated and untreated constrictor The remaining sets were made at approximately weekly intervals The serial scans comprising a set were made by scanning a 6 by 6 inch segment of the dog s precordium four times in twenty minutes while 2 to 7 5 mCi of isotope were infused intravenously at a continuously decreasing rate to provide a stable blood isotope concentration [2, 3] This plateau concentration was reached in the first three minutes of the infusion before commencing to scan Upon completing a scan the detectors were returned to the starting point and the next scan was started without delay until completion of the four scans of the set

The 36 square inches of area scanned was divided into a 960 element matrix of 30 by 32 elements With respect to time and distance the error in obtaining data from the array was less than 2 per cent The data obtained were stored on perforated paper tape [4] for entry into the Hewlett Packard 2115A digital computer at a convenient time

*Am[illegible] American Pla[illegible] [illegible] obtained from Threeco [illegible] 6779 W[illegible]verly St., M[illegible]treal, Canada.

When the scan data were entered into the computer the data were first checked for correctness relative to the location in the matrix Next a 9 point average was calculated by the computer for each of the 960 areas (0 19 x 0 2 inch) in each scan This was accomplished by summing the counts from each element with the counts from the surrounding eight and dividing by nine Because rapid serial scanning had lowered the recorded counts this spatial averaging technique was used to reduce the random count fluctuation of each element [25] The averaged data from the four scans were then used by the computer to calculate net rate of isotope uptake by computing the slope of the least squares rectilinear regression line for each of the 960 locations in the area scanned [26] These slopes are directly related to net rate of isotope uptake and the terms are interchangeable The value of Y when X = 0 was next calculated by the computer for each of the locations These are the Y intercepts

The permanent records are Polaroid Type 108 color photographs of an intensity modulated cathode ray tube display controlled by the digital computer Through digital to analog conversion 32 levels of intensity were available to modulate the cathode ray tube beam All data to be displayed are scaled from zero to 31 by the computer display program When net rate of uptake was to be photographed a red filter was placed over the camera lens For the Y intercepts a green filter was used By exposing the same frame of film to both colors (a double exposure) all the information can be seen on one color print When both red and green light impinges on the same location a shade of yellow results

Results

Orientation of the scanned area is shown in Fig 1 The close proximity of the liver has made myocardial imaging difficult using conventional methods

Under control conditions prior to constrictor placement the Y intercepts were rather even over both the atria and great vessels (Fig 2 A) With slightly higher values this same smoothness was also seen over the myocardium The liver was not visualized This same evenness was evident over the myocardium in the display of net



Fig. 1. For orientation the dot tapper record of a single scan is shown superimposed. The heart shadow from the teleroentgenogram is indicated by the dotted line. The close proximity of the liver can be seen.

rate of uptake (Fig. 2 *B*). However, the atria and great vessels were absent and the edge of the liver appeared. When both net rate of uptake and "Y" intercepts were combined in one photograph, the myocardium became yellow, the atria remained green, and the liver was the only red that was seen (Fig. 2 *C*).

Fifteen to 21 days after constrictor placement, the selected arteries had been sufficiently occluded to be detected by lower net rate of uptake (Fig. 3 *A*). Without exception, lower intercept values were evident in the same area. A few days later after collateral paths had developed, net rate of uptake would return to a pattern similar to the control. When the constrictor was on the circumflex branch of the left coronary artery and collateral paths had been shown to exist by coronary angiography, the combined net rate of uptake and the "Y" intercepts display would appear as in Fig. 3 *B*. Net rate of uptake has returned at least to the extent that no significant abnormality could be seen. The area usually supplied by the circumflex branch could still be seen as an area of red rather than yellow. One dog was studied intermittently for over a year. Each time the pattern of Fig. 3,*B* was produced.

When the anterior descending branch of the left coronary artery was selected, most dogs which survived developed short collaterals directly across the constrictor. In one dog, the collateral connections were from the distal circumflex branch to the anterior descending artery. His "Y" intercepts were good over the atria and the atrial edge of the myocardium but low over the major portion of the myocardium. This was more evident when both net rate of uptake and "Y" intercepts were seen in the same photograph (Fig. 3 *C*).

Of the 15 dogs in this study, 3 dogs with a constrictor on the circumflex branch and 2 dogs with a constrictor on the anterior descending branch lived 21 days or longer after constrictor placement. Displays of net rate of uptake and "Y" intercepts produced evidence of occlusion of the selected artery in each dog with recovery of circulation via collaterals. Coronary angiography confirmed the occlusion and presence of collaterals. Two dogs lived longer than 14 days but less than 21 days. The computer calculations and cathode ray tube displays indicated that a constrictor was on the circumflex branch of one and the anterior descending branch of the other. Negligible collateral development was evidenced. Two

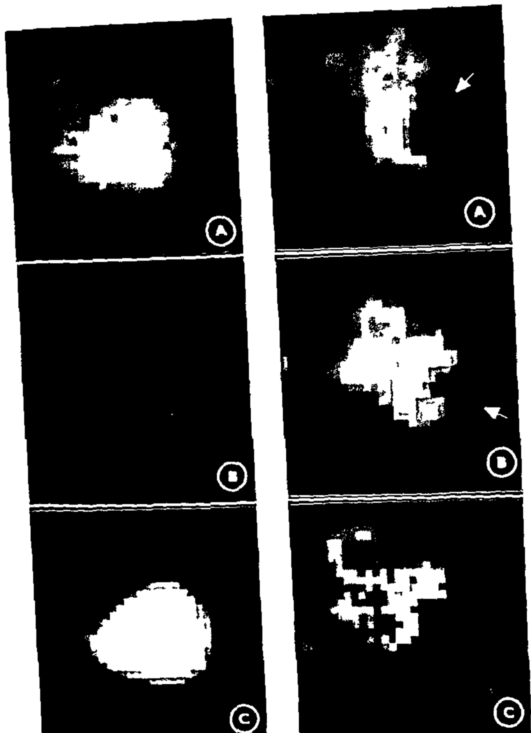


Fig 2 and 3 Fig 2 A through C A plot of Y intercept values from control dog B plot of net rate of isotope uptake from same dog C double exposu e of both display on same film The myocardium is the area in yellow Fig 3 A through C A Nineteen days after placing Ameroid constrictor on circumflex branch of the left coronary artery a dec ease in net rate of sotope uptake can be seen (ind cated by arrow) Decreased Y intercepts are al o evident in the sa e area B Ninety se en days after constrictor was placed on the circum flex b anch of the left coronary artery of another dog coronary angiography indicated collateral pathways and the combined plot of net rate of sotope uptake and Y intercept is shown The arrow points to the area u ually supplied by the circumflex branch C When the anterior descending branch of the left coronary artery wa selected for gradual occlu on thi d play pattern resulted when collateral pathways existed Little yellow i seen because the area of green and red overlap is small

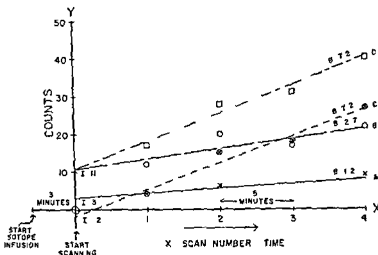


Fig 4 Actual examples of count rate—for different locations in the scanned area Using least squares regression analysis the slope (B values) of the uptake curve was calculated for each location Such a slope is directly related to net rate of isotope uptake The value of Y when X = 0 was also calculated This was used as an index to isotope appearance time and these values are referred to as Y intercept or I values Location A as shown by line A was outside the atria and myocardium Location B was a small section of the atria Location C was a small area of the myocardium which was supplied by collateral blood flow Location D was also a small portion of the myocardium but its blood supply was not compromised For more detailed explanation see text.

other dogs lived longer than 7 days but less than 14 days A constrictor was on the anterior descending branch of one and the circumflex branch of the other When compared to the control scan data displays from later scanning seemed to indicate slightly lower flow to the areas that should have been affected

Discussion

When made during a continuously decreasing infusion of ^{4}K single scans of humans have proved to correlate well with coronary angiography when coronary artery disease was rather far advanced [27] In previously referenced studies in which bolus injections of other isotopes were used positive scans were obtained only when blood flow to an area was rather severely compromised One prior study in dogs has shown that in the presence of significant collateral blood flow to a myocardial area whose primary source was gradually terminated after a bolus intravenous infusion of ^{43}K no single scans were indicative of the compromised area [33] As shown in the prior study and also in the present one when collateral flow is present net rate of uptake is useful as an indicator of returned blood flow

When blood flow has returned by a secondary path the Y intercept values can so indicate The explanation for this ability was found in Fig 4 The location which produced the counts for line A was outside the atria myocardium and liver This was really background as was shown by the low slope of 1 2 and Y intercept value of three Line B was produced by an atrial location As expected a low net rate of uptake was seen (B = 2 7) with a high intercept value of 11 Location C was over a portion of the myocardium supplied by collateral blood flow A good net rate of uptake (B = 7 2) was shown but the Y intercept was a negative 2 Location D was well removed from the prior one and its blood supply was by a *primary* unaffected path Its net rate of uptake is also 7 2 but it has a Y *intercept equal* to that of the atria

These Y intercept values are certainly directly related to the quantity of isotope in each area when scanning is begun Thus each value can be *referred to as an index* to the isotope appearance time at that location When both net rate of uptake and Y *intercepts* are shown in the same *photograph* (red and green) the following statements can be made relative to the myocardium

1 When both net rate of uptake and Y

intercepts have high values blood flow to the area is good and by an uncompromised path

2 When the net rate of uptake is high but the "Y' intercept is low, good blood flow is available but there is a delay in the appearance of the isotope

3 When both net rate of uptake and "Y' intercepts are low, the myocardium will be inactive in that area

Net rate of uptake alone may prove to be a good indicator of myocardial contractility but this has not been completely proved [9]

Can the isotope present in the chambers of the heart contribute to values of the Y' intercepts? In the atria and great vessels this is undoubtedly true to a large degree, for a plateau isotope level is being maintained in arterial blood However, in the instance where the entire myocardium had low intercept values the ventricular chambers were not evidenced (Fig 3,C) McHenry and Knoebel[30] have shown that the contribution of intracavity blood to the external myocardial counts was minimal (2 3 per cent) at 120 to 150 seconds after infusion of a bolus of ^{84}Rb With an increase in time the contribution was even less [30] Though a bolus was not the method of infusion used in the present study the maximum infusion rate did occur during the first 60 seconds in order to reach a plateau concentration in arterial blood [23] If the ventricular intracavity contribution can be discounted then those counts from areas over the myocardium must be primarily caused by emissions from the myocardium

The wide range of isotope dose was not by choice but was caused by the short half life of potassium 42 (12 4 hours) and uncertain deliveries However, use of various doses revealed that repetitive net rate of uptake results could be obtained when more than 2 mCi of ^{42}K were infused For ^{86}Rb at least 5 mCi would be required For the Y' intercept values to be statistically significant 5 mCi of ^{42}K was required These values were calculated for the moment in time which was only three minutes into the infusion and scanning period (Fig 4) Detected counts were still very low at this time A possible improvement would be to infuse for 5 minutes before starting to scan

Potassium-43 has recently become available [31] Its principal gammas are 370 keV (86 per cent), 390 keV (12 per cent) 590 keV (11 per cent) and 620 keV (81 per cent) [2] Because of the quantity of higher energy gammas that are produced using the scintillation camera may prove difficult [2] There should be no problem of its use with rectilinear scanners equipped with adequate collimators [34] For this isotope 1 5 mCi should be adequate in humans of 70 kilograms body weight The whole body dose for this amount of ^{43}K is approximately 1 05 rad, using the absorbed fraction method of calculation [31] Substitution of this isotope for those previously used should make the described procedure adaptable for use in man for myocardial scanning Even more significant information may be provided by the human heart because it is generally larger This non invasive procedure may prove to be a useful adjunct to methods of diagnosing coronary artery disease With proper isotopes and perhaps a modification of the rate of infusion could such a procedure be a means of obtaining dynamic information from other organs of the body? Further experiments will be required for an answer

Summary

Myocardial scanning with a number of isotopes was reviewed A method of mathematical analysis of serial scan data by a small digital computer was described Photographs with shades of red and green were used to display the computer output The data obtained from mongrel dogs indicate a possible usefulness of the procedure in man to determine myocardial perfusion and whether a delay in perfusion exists

We are indebted to Mrs Margaret Boyd for writing computer programs whereby a laboratory type of digital computer could be used for the mathematical calculations

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Case reports

The Guillain-Barre syndrome as a complication of the postperfusion syndrome

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The association of cytomegalovirus (CMV) infection with a clinically typical case of Guillain Barré syndrome (peripheral radiculoneuropathy, idiopathic polyneuritis) has been reported only once [1] There has been no previous report of the Guillain Barré syndrome occurring in association with the postperfusion syndrome (PPS) The purpose of this report is to describe such a relationship in a patient in whom diagnostic rises in complement fixing titers for the CMV were obtained

Case report

M D (GUH No 31839) a 47 year old man underwent open mitral valvuloplasty with extracorporeal circulation on Jan 23 1969 A rotating disc oxygenator primed with whole blood was used No intravascular prosthetic material was utilized in the surgical repair During or immediately after the procedure he received 7 units of blood one of which was less than 24 hours old His postoperative course was uncomplicated and he was discharged on Feb 2 1969 with instructions to take digitoxin 0 15 mg a day

The patient remained well until Feb 22 1969 at which time he developed chills fever and anorexia He was readmitted to the hospital on Feb 24 1969 A nontender liver was palpable 6 cm below the right costal margin and a firm nontender spleen palpable 6 cm below the left costal margin There were no cutaneous stigmas of endocarditis The neurologic examination was normal It was felt that the patient had mild mitral stenosis and insufficiency since the operation with no evidence of congestive heart failure

The hematocrit was 35 per cent with a reticulocyte count of 1 7 per cent The white cell count was 4 500 with 29 per cent segmented neutrophils 21 per cent band forms 24 per cent small lymphocytes 10 per cent atypical lymphocytes 1 per cent large lymphocytes 11 per cent monocytes and 4 per cent eosinophils The platelet count was 85 000 The lactic dehydrogenase (LDH) was 1 970 Wroblewski units the glutamic pyruvic transaminase (SGPT) 30 Karmen units the alkaline phosphatase 0 9 Bessie Lowry units and the bilirubin 1 0 mg total and 0 1 mg per 100 ml direct

The hospital course was characterized by continued fever chills and diaphoresis although at no time was the patient clinically toxic Repeated cultures including cultures for L forms were persistently negative By March 8 1969 the hematocrit had dropped to 33 5 per cent with a haptoglobin of 8 mg per cent the serum iron was 90 micrograms per 100 ml the total iron binding capacity (TIBC) 274 micrograms per 100 ml and the Coombs test 1+ There were repeatedly negative stool guaiacs The white cell count rose to 10 700 with 24 per cent segmented neutrophils 3 per cent band forms 56 per cent small lymphocytes 15 per cent atypical lymphocytes 1 per cent monocytes and 1 per cent eosinophils Hepatosplenomegaly remained unchanged Serial sera for febrile and heterophile agglutinins did not demonstrate any change in titers The com-

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plement fixation titer for CMV on February 25 was 1 2 On March 9 1969 the patient became afebrile and remained so for the next three days During hospitalization urine blood and sputum samples were obtained for viral cultures

On March 12 1969 the patient was discharged from the hospital with a diagnosis of postperfusion syndrome His medications included only digoxin 0 25 mg a day and chlordiazepoxide 10 mg three times a day

The patient did well until the fourth week in March when he began noting paresthesias of the soles of the feet and legs which ascended to involve the lower trunk fingers hands and arms This was followed by progressive weakness ascending from the lower extremities to involve the upper extremities On April 3 1969 he noted some difficulty in swallowing and some hoarseness with numbness of his tongue On April 5 1969 he was readmitted to the hospital

The cardiac examination was unchanged from the previous admission A nontender liver was palpable 6 cm. below the right costal margin and the spleen was felt 6 cm. below the left costal margin Sensory examination demonstrated hypesthesia to touch and pinprick to the midcalf bilaterally Motor examination demonstrated bilateral leg paresis the left greater than the right and more prominent proximally There was marked bilateral drift of the outstretched arms The tendon reflexes were absent in the arms and the legs and there were no pathologic reflexes

Laboratory data included a hematocrit of 41 per cent with a reticulocyte count of 2 9 per cent The white cell count was 7 700 with 47 per cent segmented neutrophils 44 per cent small lymphocytes 7 per cent monocytes 1 per cent eosinophils 1 per cent atypical lymphocytes The blood urea nitrogen was 16 mg per 100 ml glucose 88 mg per 100 ml The electrolytes were within normal limits The glutamic oxalacetic transaminase (SGOT) measured 51 Karmen units glutamic pyruvic transaminase (SGPT) 70 Karmen units bilirubin 0 9 mg per 100 ml calcium 11 mg per 100 ml (repeat 10) and phosphorus 3 8 mg per 100 ml Serum levels of arsenic and lead were normal On protein electrophoresis the albumin was 3 85 Gm. per 100 ml alpha 1 globulin 0 49 Gm per 100 ml alpha 2 globulin 0 79 Gm. per 100 ml beta globulin 1 24 Gm per 100 ml and gamma globulin 1 83 Gm per 100 ml Febrile and heterophilic agglutinins were negative a cold agglutinins titer of 1 128 was obtained A lumbar puncture was performed which showed normal dynamics Examination of the cerebrospinal fluid showed one white cell and one red cell per cubic millimeter with a protein of 145 mg per 100 ml

Over the subsequent 9 days he became progressively weaker with a decrease in his vital capacity On April 14 1969 a tracheostomy with assisted mechanical respiration was required to maintain adequate ventilation. Starting on April 20 he was progressively weaned off assisted respiration and by April 28 he had become afebrile and was able to maintain adequate vital capacity off the respirator The remainder of the hospital course was characterized by progressive improvement in motor function which returned completely to normal by May 23 when he was discharged from the hospital

During the hospital course blood urine and sputum cultures were obtained for viral studies but no viruses were recovered However the CMV complement fixing antibody titer performed in duplicate rose from 1 2 on February 25 to 1 128 on April 6 with simultaneous testing

Discussion

The occurrence of fever splenomegaly and atypical lymphocytosis in a patient 2 to 7 weeks following cardiopulmonary bypass is now well recognized as the postperfusion syndrome[2,3] Our patient demonstrated all the classic features of this syndrome Isolation of cytomegalovirus from the urine sputum or blood of patients with the postperfusion syndrome, along with rising complement fixation titers to CMV has been reported by several authors[4-11] It is the prevailing concept that the PPS is associated with primary CMV infection or infection with a strain of CMV antigenically unrelated to one to which the patient may have been previously exposed Also reinfection with an identical or antigenically related type may be associated with an asymptomatic rise in titer The mechanism of infection is thought to be through transfusion of fresh (less than 24 hours old) blood used at surgery or in the intraoperative period[10-12]

Despite the fact that we were unable to isolate CMV from urine blood or sputum of our patient serologic studies did demonstrate a significant[8] rise in CMV complement fixing antibody titer from 1 2 to 1 128 Although the PPS is considered to be benign our patient developed a serious complication the Guillain Barre syndrome

Approximately 50 per cent of the cases of Guillain Barré syndrome have been associated with an antecedent infectious illness However a specific infectious agent has been demonstrated in only a minority of these cases Although the exact pathogenesis of the syndrome is unknown some authors[13] feel that the infectious agent involved indirectly stimulates the host s immunologic mechanism to attack the Schwann cell

Idiopathic polyneuritis has been reported to occur following surgery[14-1] Arnason and Asbury[14] reported six such cases and postulated that during surgery release of nerve tissue antigen occurs which in association

with unknown host factors leads to an immunologic response resulting in polyneuritis. Two of the cases reported by these authors had received blood transfusions, but no mention is made whether any of the units received were less than 24 hours old. Where is the interval between surgery and polyneuritis in Arnason and Asbury's patients ranged from 1 to 4 weeks our patient developed his first symptoms of peripheral radiculoneuropathy at least 8 weeks after surgery but 4 weeks after the onset of symptoms of the PPS.

Klemola and associates[1] described a 27 year old man who developed a typical Guillain Barré syndrome approximately 3 weeks after a short febrile illness. There was no change in antibody titer to all common viruses except to CMV, to which there was a rise in complement fixing antibody titer from 0 to 1 per 64. In addition, these authors were able to isolate from the patient's urine a cytopathic agent with the characteristics of CMV. Although these authors did not explicitly infer an etiologic relationship between CMV and the Guillain Barré syndrome such an association is implied.

The above report describes a typical Guillain Barré syndrome in a patient with the postperfusion syndrome and immunologic evidence of a recent cytomegalovirus infection. The Guillain Barré syndrome represents a previously unreported complication of the postperfusion syndrome. The relationship between the Guillain Barré syndrome and cytomegalovirus infection remains speculative. However, the well recognized neonatal syndrome with central nervous system manifestations secondary to intrauterine infection with CMV as well as the association of the Guillain Barré syndrome with other viral[1,16] and mycoplasma[17,18] infections seems to make this speculation tenable.

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Ventricular fibrillation precipitated by carotid sinus pressure Case report and review of the literature

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Since Hering s[1] studies in the 1920 s which clearly established the reflex circulatory effects of carotid sinus nerve stimulation the carotid sinus nerve and reflex have been increasingly employed in the diagnosis and treatment of various dis orders Carotid sinus pressure (CSP) has been invaluable in the elucidation of the underlying mechanism and prompt treat ment of various supraventricular tachy arrhythmias as well as in their differentia tion from ventricular arrhythmias Stimu lation has more recently been used to elicit early signs of digitalis toxicity [2] relieve acute pulmonary edema [3,4] confirm the diagnosis of angina pectoris [5] provide symp tomatic relief of angina [6] and treat various forms of hypertension [7] CSP when per formed by the recommended technique and with the usual precautions [2] is generally a safe procedure The rare development of neurologic deficits after CSP has been widely publicized though the mechanism appears to be transient carotid occlusion in patients with already compromised cere bral circulation[8] rather than a direct effect of reflex changes. Several well-documented cases of life threatening ventricular ar rhythmias and atrioventricular (A V) con duction defects resulting from CSP have appeared in the literature but this danger continues to be little appreciated This case report documents the appearance of ven tricular tachycardia (VT) and fibrillation (VF) following CSP

Case report

A 66-year old man was admitted to the Peter Bent Brigham Hospital for elective resection of a sigmoid polyp In 1950 the patient pre ented poly arthritis flexion contractures of his hand ulcerated fi gertips Raynaud phenomenon and progres ive dysphagia Histologic material confirmed the clinical impression of systemic sclerosis Attempts at pal liation of symptom with right transthoracic dor al sympathectomy and corti one therapy we e un succes ful The patient first noted palpitation ac companied by left shoulder and neck pain in 1960 An electrocardiogram (ECG) during one of these epi odes revealed atrial flutter Desp te digitaliza tion the patient continued to have recurrent palpi tation The patient was admitted to the hospital in 1966 and again in 1967 for management of his atrial arrhythmias Physical examination was unremark able except for labile hypertension the external manifestations of scleroderma and a Grade II/VI apical systolic ejection murmur Chest x ray re vealed left ventricular enlargement Adm sion ECG showed non pecifi ST T abnormal tie and occa onal atrial and ventricular premature beats During both hosp talizations supraventricular tachy cardia (SVT) with 1 1 and 2 1 A V conduction was observed On one occasion CSP produced a transient

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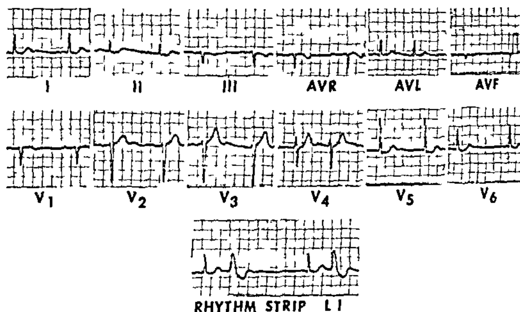


Fig 1 Admission ECG showing sinus rhythm with atrial and ventricular premature beats.

complete A V block without untoward incident Results of blood tests were normal including blood urea nitrogen (BUN) 21 creatinine clearance 120 c c per minute T_4 8 8 μg per cent and T_3 resin uptake 36 per cent At the time of cardiac catheterization a resting left ventricular end diastolic pressure of 22 mm Hg and an insignificant 13 mm aortic valve gradient were documented Coronary arteriography revealed a 75 per cent stenosis of the proximal right coronary artery

Control of the paroxysmal SVT was attempted with 200 mg of quinidine sulfate four times a day and with propranolol in doses ranging up to 480 mg per day with varying success In 1968 the patient noted the onset of exertional angina ECG at this time was unchanged except for the development of first degree A V block On Oct 18 1970 because of rectal bleeding and x ray visualization of a sigmoid polyp the patient was readmitted to the hospital On admission his daily medications included 0 25 mg of digoxin per day 200 mg of quinidine three times a day and 120 mg of propranolol four times a day for arrhythmia prophylaxis and 500 mg of alpha methyldopa three times a day for control of mild hypertension Admission ECG (Fig 1) showed first degree A V block (P R interval 0 24 sec) frequent atrial premature beats short runs of ventricular bigeminy clockwise rotation in the chest lead and nonspecific ST T abnormalities All medications were stopped on admission However on Oct 20 he received 0 25 mg of digoxin and on Oct 21 just before the operation 0 125 mg intramuscularly The operation and initial postoperative course were uneventful On Oct 22 he received 0 25 mg of digoxin intramuscularly Two ECG s taken during the first 24 hours after the operation showed no additional diagnostic changes Results of blood tests were normal including BUN 15 and serum potassium 4 7 During the afternoon of the first post operative day the patient suddenly developed anginal discomfort unrelieved by sublingual trinitroglycerin. ECG at this time (Fig 2) showed a SVT with ventricular response of 186 CSP defined the mechanism to be an A V junctional tachycardia (see Discussion) but then precipitated further arrhythmias which prompted this report After CSP the atria began to fibrillate but before the return of stable atrioventricular conduction the patient developed VT and VF successfully eliminated by a 400 watt second DC countershock with the subsequent appearance of atrial fibrillation and an appropriate ventricular response Daily ECG s after the defibrillation demonstrated no serial change Enzyme abnormalities were difficult to interpret because of the recent abdominal operation and DC counter shock After the defibrillation the patient complained of heaviness and numbness in the right foot and for the first time was noted to have absent pedal pulses An arteriogram confirmed obstruction of the right anterior and posterior tibial arteries Reconstructive surgery was unsuccessful and the patient underwent amputation below the right knee He was subsequently discharged on 0 25 mg of digoxin per day 15 mg of propranolol four times a day and 300 mg of quinidine four times a day

Discussion

The extensive review of CSP by Lown and Levine in 1961 stated permanent cessation of the heart beat or serious ventricular arrhythmias are almost unheard of They correctly considered Shookhoff case[9] of VF to be artifact Multiple or multifocal ventricular extrasystoles precipitated by CSP but not progressing to VT or VF have been described by several investi

gators[10,13] Wenckebach and Winterberg[19] and later Scherf and Schott[13] reported the case of a woman with recurrent palpitation in whom CSP precipitated what the authors considered to be VT which in turn was promptly terminated by repeat CSP However that CSP precipitated a rapid SVT with aberrant conduction which was then abolished with restoration of sinus rhythm by a second application of CSP is an alternative explanation Most of the more recently documented episodes of VT or VF following CSP have occurred in ill patients with either refractory supraventricular tachyarrhythmias or CHF for which large parenteral doses of digitalis have been rapidly administered[11 0 3] Franke[4] does not indicate whether his 60 year-old patient with arteriosclerotic heart disease and long standing atrial flutter with varying A V block who developed a burst of four ventricular flutter like complexes after the initiation of CSP was taking digitalis However it is important to note that four patients [27] ranging in age from 35 to 55 years with paroxysmal SVT but no other evidence of heart disease also developed VT following CSP Other published cases of ventricular tachyarrhythmias following CSP[8 9] supply no clinical information The present case documents clearly the potentially lethal effect of CSP While recuperating from an uneventful abdominal operation at a time when serum electrolyte levels were normal and small daily maintenance digoxin doses were being irreguarly administered as detailed above in the case history the patient developed a SVT with 1 1 A V conduction (Fig 2) associated with anginal pain CSP produced the expected A V block revealing inverted P waves in Lead II suggesting that the underlying mechanism was an A V junctional tachycardia Discrete P waves are not seen in the subsequent strips and the irregular base line probably represents atrial fibrillation Instead of resumption of A V conduction an idioventricular escape focus fired first slowly and then more rapidly though aberrant conduction of supraventricular beats cannot be totally excluded A second focus produced a short burst of VT This was followed by multifocal ventricular beats from at least three different foci Four of the first five ventricu

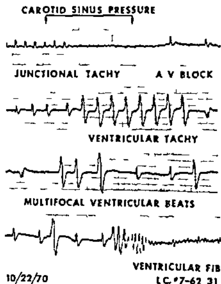


Fig 2 Continuous recording of Lead II An A V junctional tachycardia is revealed during the application of CSP Before the re-establishment of a supraventricular rhythm with stable A V conduction ventricular tachycardia and fibrillation ensue See text for detail

lar beats of the fourth strip were from the same focus the sequence being interrupted by the third complex which appeared after an interectopic interval of 0 40 sec After the fifth complex a different focus again fired an impulse with a shorter interectopic interval of 0 32 sec which fell in the vulnerable period of the preceding beat and triggered off VF

The mechanisms of ventricular tachyarrhythmia resulting from CSP and other vagus stimulating maneuvers[30 31] are not clear Despite the prevailing view to the contrary the mammalian ventricle does appear to be directly influenced by vagal stimulation There is now impressive morphologic hemodynamic and pharmacologic evidence to support the concept that the canine ventricle possesses cholinergic vagal innervation Using electron microscopy Napolitano and co workers[32] have demonstrated the persistence of neural elements C fibers in the myocardium of the chronically denervated canine ventricle These

nerves must arise from ganglion cells within the heart and therefore, by definition, are postganglionic. These fibers are essentially devoid of catecholamine containing granules. Although not explicitly proved, it is reasonable to consider these neural elements to be parasympathetic. Jacobowitz and associates[33] have demonstrated the presence of acetylcholinesterase in cat ventricular muscle. In very carefully controlled isolated ventricular and whole heart preparations which eliminate the possible indirect effect on the ventricle of a depression of atrial performance, numerous investigators[34-36] have demonstrated the direct negative inotropic effect of vagal stimulation on ventricular myocardium. Levy and associates[37] demonstrated that increased vagal tone as part of the carotid sinus reflex produced a negative inotropic effect on the left ventricle. Blumenthal and associates[35] have shown that intracoronary acetylcholine (ACh) can have a negative inotropic effect as well. There is no reason to suspect that the human ventricle is not similarly innervated. It may be that those patients experiencing difficulty after CSP have an unusually rich ventricular cholinergic innervation. Despite the usual muscarinic effects of the vagal neurotransmitter ACh, a stimulatory effect on atria and ventricles has been well documented in animal experiments. Scherf and Chick[39] have produced atrial flutter and fibrillation by direct ACh application to the sinus node, and Loomis and Krop[40] have produced similar results with vagal stimulation after pretreatment with anticholinesterase. In 1897 Knoll,[41] recording direct arterial pressure and ventricular contraction curves in dogs, rabbits, and pigeons, noted that stimulation of the distal stump of the vagus nerve elicited ventricular flutter and fibrillation as an aftereffect soon after the cessation of vagal stimulation. Scherf in early studies and later with co-workers has elicited VT and VF in the dog by vagal stimulation after either aconitine injection[42] or application of hypertonic saline to the ventricular epicardial surface[43] as well as by direct focal application of ACh to the ventricular surface.[39] ACh accumulation in proximity to ventricular muscle and Purkinje fibers might thus be expected to stimulate ectopic foci and tachyarrhythmias in man.

After the release of CSP there is a recognized rebound sympathetic stimulation. Other than reflex changes, Middleton and colleagues[44] proposed more than twenty years ago that vagal stimulation caused the release of an epinephrine-like substance in the myocardium. Recently Blumenthal and colleagues[35] demonstrated that intracoronary ACh in the atropinized dog had a positive inotropic effect which could be neutralized by pretreatment with beta adrenergic blocking agents. The catecholamines released during vagal stimulation appear to come from myocardial stores other than those of the sympathetic nerve endings.[4] Excess myocardial catecholamines asymmetrically distributed will contribute to the genesis of ventricular tachyarrhythmias. Han and co-workers[46,47] have demonstrated that sympathetic nerve stimulation increases the temporal dispersion of recovery of excitability in ventricular muscle, setting the stage for re-entrant excitation and subsequent VF.

Other factors possibly contributing to the genesis of CSP-initiated ventricular arrhythmias deserve mention. Decreased heart rate resulting from CSP-induced AV block is itself associated with increased asynchrony of recovery of excitability of ventricular muscle.[48] Myocardial ischemia, often clinically manifest as angina pectoris, may result from the increased myocardial oxygen needs during a SVT and is itself a cause of asymmetric repolarization and possible re-entrant arrhythmias.[46] Lastly, increased pacemaker activity resulting from a lower extracellular myocardial potassium concentration secondary to asystole or period of slow heart rate may play a role in initiating arrhythmias.[49]

Increased efferent vagal stimulation and increased catecholamine release appear to be largely responsible for the CSP-induced ventricular arrhythmias. Regardless of the mechanism, the danger of precipitating a life-threatening arrhythmia with CSP definitely exists. Although these arrhythmias may occur more commonly in the very ill patient treated with digitalis excess, they also are seen in the young patient with re-

current supraventricular tachyarrhythmia and no other evidence of heart disease The clinician should be aware of this potentially lethal side effect albeit uncommon and be prepared to treat it appropriately

Summary

Carotid sinus pressure (CSP) is used often for both therapeutic and diagnostic purposes Despite its low incidence of attendant complications CSP can cause fatal arrhythmias A case report of VT and VF resulting from CSP is presented and the literature is reviewed The mechanism is unknown but it is suggested that increased vagal tone and possible vagal mediated catecholamine release may stimulate ventricular ectopic foci with the subsequent production of tachyarrhythmias Knowledge of the potential complications of CSP and the ability to treat them is necessary to safeguard patient safety

I would like to thank Dr R Gorlin for permission to report his patient and Drs David Scherf and Jules Cohen for their critical evaluation of the ECGs

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Clinical pathologic conference

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Case report

This 7-month-old Caucasian boy with left-sided hemiparesis was transferred from an outside hospital to the University of Illinois Neuropsychiatric Institute on January 5, 1965. The history of the present illness dates back to an episode of high fever of unknown origin. He was hospitalized at the time but the date and the details of this hospitalization were not obtainable. The patient developed a second episode of fever on November 6, 1964, and was again hospitalized. Clinical and x-ray examinations revealed a right upper lobe bronchopneumonia. The infant was treated with antibiotics and was discharged fully recovered on November 14, 1964. Eleven days after this the infant was rehospitalized with vomiting, a temperature of 105° F., and lethargy. A consultant's notes at the time described a sickly infant weighing 12 pounds, 8 ounces, 2 pounds less than at the previous discharge. Head circumference was 40.8 cm. Pulse was 120 beats per minute. The eyes and head were deviated to the right. The pupils were round and equal. Examination of the ears revealed a minimal amount of injection of the left tympanic membrane with some retraction of both tympanic membranes. The nose and throat were not remarkable. The chest was clear. The heart tones were normal. There was a Grade I ejection murmur at the left sternal border. The abdomen was soft with no palpable organs or masses. Femoral pulses were clearly felt bilaterally. Neurological examination revealed a questionable Moro reflex and a 1+ tonic neck reflex on the right. On the left side there was a poor tonic neck reflex. There were absent cremasteric, questionable abdominal and questionable hyperactive deep tendon reflexes. Laboratory examination revealed a normal level of blood urea nitrogen and of serum calcium. A spinal tap, bilateral subdural taps, and a pneumoencephalogram were performed yielding no abnormal findings. X-rays of chest, skull, spine, abdomen, and intravenous pyelogram were all within normal limits. However, an electroencephalogram revealed a focal slowing and spiking over the right hemisphere and paroxysmal slowing of lesser degree over the left hemisphere.

The patient was again treated with antibiotics. His neurological condition remained unchanged. He was then transferred to this institution.

Past history. The patient weighed 7 pounds, 1 ounce at birth and was the product of a full-term pregnancy. Delivery was uncomplicated. The infant had a normal neonatal course.

Family history was not remarkable.

Physical examination. On admission the infant was fairly well nourished with evident recent weight loss. He was pale and appeared chronically ill. Temperature was 99°, pulse was 120 beats per minute, respirations were 30 per minute. Head circumference was 40.8 cm., chest circumference was 38 cm., abdominal circumference was 37 cm., weight was 13 pounds, 4 ounces. Ears, nose, and throat were clear. The neck was supple. The chest was clear to percussion and auscultation. There was no evidence of cardiomegaly. Heart sounds were normal; no murmurs were heard. The abdomen was generally distended, more so centrally than in the flanks. No free fluid was present. The iliac fossae were normal. The abdominal wall was tense on palpation and wincing was elicited, suggesting moderate tenderness of what was made out to be a midline hypogastric mass. The umbilicus was prominent but not everted. Widespread central pulsations were noted and a systolic bruit was clearly audible over the central abdominal area. The mass was approximately 8 cm. in diameter and rounded in shape. It was minimally mobile with ill-defined edges and was apparently not attached to the overlying skin, liver, spleen, or either kidney. The genitalia and scrotum were normal. Both testes were descended. The liver was palpated 2 cm. below the costal margin on the right side. The tip of the spleen could be felt. Rectal examination was not remarkable. The spine was

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normal. The left femoral pulse was easily felt but the right femoral pulse was weak. The pulses in the arms were synchronous and of good volume. Systolic blood pressure by the flush method was 70 mm. Hg in the right and left arm, 60 mm. Hg in the right leg, and 70 mm. Hg in the left leg. No lymphadenopathy was detected. Neurological examination revealed the fingers of the left hand to be held in flexion. The left leg was in semiflexion. Both limbs on the left had increased muscular tone with increased tendon reflexes. Sensation of the limbs on the left appeared to be intact. The grasp reflex in the left hand was weak and poor. The eyes were deviated to the right side, as was the head. A slight facial palsy was evident on the left side. The pupils and fundi were normal. The anterior fontanelle was normal, open, and soft. No nuchal rigidity was present. The tongue was deviated to the left. The right-sided extremities were normal.

Laboratory data. On admission a hemogram revealed moderately severe anemia with a hemoglobin of 6.8 Gm. per cent, hematocrit 28, and red cells 3.36 million per mm.^{3} Reticulocytes 1.9 per cent, platelets 104,832 per mm.^{3}, white cells 14,600 per mm.^{3} The differential white cell count was within normal limits. Bone marrow examination revealed erythroid hyperplasia with no abnormal elements. Urine analysis was normal. Blood urea nitrogen was 14 mg. per cent, serum calcium 5 mEq. per liter, alkaline phosphatase 1.7 Bodansky units, serum acid phosphatase 0.6 units, fasting blood sugar 108 mg. per cent, cholesterol 170 mg. per cent, total serum proteins 6.8 Gm. per cent with albumin 4.7 Gm. per cent and globulin 2.1 Gm. per cent. Vanillyl mandelic acid (VMA) excretion was 1.1 mg. in 24 hours. Throat culture grew pneumococci; urine culture grew moderate numbers of Klebsiella and E. coli. Stool culture was negative for pathogens. Lumbar puncture revealed an opening/closing pressure of 170/150 mm. H_2O. The cerebrospinal fluid was clear and colorless with no cells. Cerebrospinal fluid glucose: not sufficient quantity; protein 24 mg. per cent, chloride 130 mEq. per liter. There was no growth on culture of the cerebrospinal fluid. Roentgenologic examination revealed no abnormality of the chest. A skeletal survey was normal, as was the skull. Multiple views of the abdomen revealed a normal pattern of distribution of intestinal gas. The abdominal mass was not outlined. An electroencephalogram was abnormal with markedly reduced amplitude and a slow wave focus over the right cerebral hemisphere. Intravenous pyelogram revealed slight superolateral displacement of the left renal pelvis.

Hospital course. The patient ate poorly throughout most of his hospitalization. On January 8 the edge of the liver was palpated 3 cm. below the right costal margin. Both femoral pulses were now diminished. The patient was given a transfusion of packed red blood cells. On January 11 the patient underwent aortography via a left femoral cutdown. Injections in the ascending aorta and in the mid descending aorta were performed. These showed an orange-sized cavity filling with dye at the level of the aortic bifurcation. The left iliac artery was visualized but that on the right was not. A catheter could not be introduced into the inferior vena cava via the left saphenous vein. A hand injection showed no direct communication with the inferior vena cava but numerous venous collaterals. Cerebral angiography at this time showed normal left but nonvisualizing right middle and posterior cerebral vessels with poorly visualizing anterior vessels. Following catheterization the patient was placed on penicillin and kanamycin since he developed a brief elevation of temperature to 10? F. The patient was given a second transfusion which raised the hematocrit from 25 to 32. This was followed by an exploratory laparotomy on January 21, at which time a solid mass was found attached to the lower pole of the left kidney and extending obliquely to the right lower quadrant. The mass was adherent to the terminal aorta and was there associated with a pulsatile sac. A biopsy of the mass was taken for frozen section. The postoperative course was uncomplicated until 11 P.M. on January 23, when the patient became pale with abdominal distension and absent bowel sounds. The hematocrit was 20. Blood samples for electrolytes drawn on January 20 and January 23 were within normal limits. In the next 30 hours he received 450 c.c. of whole blood, raising the hematocrit to 30. On January 25 the urinary output, previously adequate, fell to 40 c.c. in 24 hours. At 1:50 A.M. on January 25 the patient had generalized convulsions which were controlled with paraldehyde and intravenous calcium gluconate. Respiration, however, remained irregular and he was pronounced dead a few hours later.

Discussion

DR. ROSENTHAL. The patient, a 7 1/2 month old boy with a left hemiparesis, was transferred to the University of Illinois Medical Center on January 5, 1965 from another hospital. The original illness apparently began with fever, and the details are somewhat vague. The patient developed a second episode of fever on November 6, 1964 and was again hospitalized with a diagnosis of bronchopneumonia involving the right lung. The infant was treated with antibiotics and discharged. Eleven days later on November 25 the child was rehospitalized with vomiting, high fever, and lethargy. He weighed 12 pounds, which is in the 3rd percentile for his age. The head circumference was 40.8 cm., which is also in less than the 3rd percentile. Femoral pulses at the time were palpable bilaterally. There were abnormal neurologic findings: the eyes and head deviated to the right, there was a questionable Moro reflex and a 1+ tonic neck reflex on the right. At the age of 7 months these reflexes should no longer be present.

The neurologic signs suggest the possibility of encephalitis. The fever and leth

argy are compatible with the diagnosis and the negative lumbar puncture does not exclude the diagnosis A subdural tap was done which was normal It seems unlikely that a subdural hematoma would be present in association with a small head and a small flat fontanel The electroencephalogram was of interest There was focal slowing and spiking of the right hemisphere and paroxysmal slowing of the left hemisphere The abnormality is not the diffuse type of slowing which is found in encephalitis but it suggests that an organic process of diffuse etiology was present compatible with the physical signs

On transfer to the University of Illinois Hospital the infant was found to be acutely ill The blood pressure was normal There was evidence of recent weight loss The left hand and the left leg were held flexed with increased muscle tone and increased tendon reflexes The grasp of the left hand was weak and a slight left facial paresis was present indicating a left hemiparesis The eyes were deviated to the right These findings suggest diffuse brain involvement Although the original findings were compatible with encephalitis the newer localizing findings now suggest the possibility of vascular disease perhaps carotid arterial thrombosis Angiographic studies indicate that carotid thrombosis is not as uncommon in small children with acute illness as was previously believed

The abdominal findings were of great interest On examination the abdominal wall was tense on palpation and pain was present A midline hypogastric mass was present Widespread central pulsations were noted and a systolic bruit was clearly audible over the central abdominal area The mass was large measuring 8 cm in diameter with ill-defined margins It was slightly mobile and not attached to the overlying skin The left femoral pulse was easily palpable but the right femoral pulse was now weak The abdominal mass apparently had developed rapidly

Several possibilities should be considered The first is tumor Wilms s tumor is a possibility since this tumor arises in the kidney and can metastasize to the lungs and brain The localization of the mass in the midline however is against the diagnosis—as are the pulsations and bruit The normal intravenous pyelogram almost completely excludes this diagnosis

Neuroblastoma the most common abdominal tumor in childhood should also be considered This tumor frequently originates in the adrenal but can develop anywhere along the sympathetic chain In many instances it is not possible to locate the primary Neuroblastomas metastasize to bone including frequently the orbit and skull and producing increased intracranial pressure Occasionally they metastasize to the brain However this tumor does not pulsate and does not have a bruit In addition the normal excretion of VMA is strongly against this diagnosis In about 90 per cent of neuroblastomas there is increased excretion of VMA in the urine Neuroblastomas synthesize norepinephrine and the principal degradation product of norepinephrine is VMA

We must also consider a retroperitoneal teratoma This tumor is fairly common and often has spotty areas of mineralization Teratomas do not pulsate nor do they have a bruit and such a tumor in this case is therefore unlikely There are other retroperitoneal malignancies such as lymphomas and rhabdomyosarcomas but none of them pulsate nor are they associated with bruits

Elaborate roentgenographic studies were performed by Dr Hastreiter and his colleagues to determine the nature of the mass It is essential that the films be reviewed

DR HASTREITER The interpretation of selective angiograms is as follows

1 *Abdominal aorta anteroposterior* The lower segment of the abdominal aorta is displaced to the left and curved i e convex toward the left side At the level of its bifurcation there is a rounded cavity filled with contrast material This cavity is directly connected to the aorta There is no visualization of the right common iliac artery (Fig 1)

2 *Abdominal aorta left lateral* There is marked posteroanterior displacement of the aorta with anterior convexity as if the vessel had been pushed from behind The large cavity described on the anteroposterior view almost reaches the anterior wall of the abdomen

3 *Right femoral vein anteroposterior* This injection shows complete obstruction



Fig. 1. Aortogram demonstrating radiopaque material in the pseudoaneurysm or oval structure which displaces the lower abdominal aorta to the left. Note the catheter leading into the patent left iliac vessels and the absence of filling of the right iliac vessels.

of the inferior vena cava, the contrast material specifying a network of collaterals, mostly of the paravertebral plexus.

4. *Cerebral angiogram.* This finding was as described in the preliminary presentation.

STUDENT: Is the abdominal mass a single large cavity or multiple cavities?

DR. HASTREITER: It appears to be one large cavity.

DR. ROSENTHAL: We note that the intravenous pyelogram shows displacement of the kidney. There is no malformation of the calyces as might be seen in a patient with Wilm's tumor. In neuroblastomas displacement may be seen, but as we have noted there are strong points against the presence of this tumor. The films indicate that the cavity appears to be filled with blood. The right iliac artery and the inferior vena cava appear to be thrombosed. At surgery a mass was found below the lower pole of the kidney extending to the right lower quadrant. A malignant tumor extending into the aorta, eroding its wall and causing aneurysm remains a possibility. So, too, does a primary disease of the aorta with development of an aneurysmal sac, possibly even with rupture and organizing hematoma.

It is essential to review the possibilities for disease of the aorta of this nature. Takayasu's disease usually involves the arch of the aorta and its branches. Danaraj and Wong[1] however, have pointed out recently that the abdominal aorta may be involved in this condition. In Takayasu's disease panarteritis develops with stenosis of various visceral arteries. Thromboses occur with extensive destruction of the media. The vasa vasorum frequently are obliterated. Against this diagnosis, however, is the age of the patient. Takayasu's disease has not been reported to occur in infants. Aneurysms also do not occur in this disease.

A dissecting aneurysm should be considered. The site would be most unusual for it is too inferior. The patient has none of the signs of Marfan's syndrome commonly associated with dissecting aneurysm. Coleman[2] some years ago reported a 10 year-old girl with dissecting aneurysm which he attributed to a primary disease of the media. There are four other reported cases ranging in ages from 1 to 10 years.

Homocystinuria is a metabolic disease associated with vascular thrombosis. In this disease thrombosis may occur in medium sized arteries and veins such as coronary vessels, renal veins, cerebral veins and arteries, and arteries of the extremities. There are no reported cases in infancy with vascular thrombosis. Aneurysm does not occur.

Also to be considered is a primary bacterial infection of the aorta. In this age of antibiotics this would be a most unusual condition.

One must also consider the possibility of a diffuse disease involving the arteries of this patient. A frozen section was taken at surgery but we do not have the report.

DR. KARACHORLU: Frozen sections were reported as fibroadipose tissue with chronic inflammation.

DR. ROSENTHAL: Was there an electrocardiogram on this patient?

DR. HASTREITER: The electrocardiogram was normal.

DR. ROSENTHAL: We should consider conditions which can cause involvement of many major vessels. A diffuse vascular disease could explain the cerebral symptoms and the involvement of the aorta. One must consider the possibility of polyarteritis nodosa. This disease is not common. It is

difficult enough to diagnose in adults but even more difficult in infants since the arteries of the skin and muscles in infants are rarely involved Can polyarteritis occur in a patient 7 months of age? The literature has been reviewed by Roberts and Fetterman[3] There were 20 cases in children under two years of age including 2 of their own The vessels involved were the splenic renals the superior mesenteric the iliacs the coronaries the pulmonaries and the vessels to the extremities Pulmonic involvement was frequently present It is of interest that our patient showed some pulmonary disease Nervous system involvement was not uncommon with the development of flaccid paralysis and convulsions Aneurysmal dilatation of the coronary vessels with perforation was reported in some cases I would postulate that our patient did have generalized arterial disease inflammatory in nature I postulate involvement of cerebral vessels perhaps the right internal carotid The iliacs and femorals are also involved by thrombosis and the aorta appears to have been involved with development of an aneurysm with rupture followed by an organizing hematoma Obstruction to the vena cava apparently is present from the roentgen studies It is unusual to have involvement of the venous system in polyarteritis and perhaps obstruction from the mass is responsible for the failure to visualize the vena cava

I therefore postulate that this patient had a diffuse arterial process involving several vessels including the aorta and that aneurysm of the aorta was responsible for the aneurysmal mass I think that there is a strong possibility that polyarteritis nodosa underlies this condition Whatever the cause the condition is certainly most unusual and accounted for the great difficulty in arriving at a diagnosis

STUDENT Is congenital syphilis a possibility?

DR ROSENTHAL Diffuse arterial involvement and aneurysmal development would be most uncommon in congenital syphilis Bone involvement is common and would have been detected by roentgen examination

STUDENT If this infant had polyarteritis nodosa are you not concerned by the lack of renal disease and hypertension?



Fig 2 The pseudoaneurysmal sac opened posteriorly Note that the aneurysm encloses the distal aorta and the common iliac arteries The thrombotic right common iliac artery with roughened intimal surface can be seen immediately beyond the bifurcation.

DR ROSENTHAL I am However in young infants as pointed out by Roberts and Fetterman[3] it is not uncommon to have polyarteritis nodosa with no renal involvement Polyarteritis nodosa is such a diffuse disease that the symptoms depend upon the specific vessels involved

DR KARACHORLU At autopsy the abdominal cavity contained 200 c c of blood There was extensive retroperitoneal hemorrhage A large mass in the lower abdomen measured 6 by 7 cm It was in the midline and attached to the vertebrae Its outer surface was covered by a thick layer of recent blood clot The lower portion of the abdominal aorta and both common iliac arteries were surrounded by this mass On careful dissection the mass was found to be a false aneurysmal sac filled with blood clot The wall measured up to 1 mm in thickness with an outer fibrous component The lower portion of the aorta its bifurcation and both common iliac arteries were within the false aneurysmal sac (Fig 2)



Fig 3 Section through right common iliac artery close to the necrotic area Thrombus overlying the thickened intima is seen in the left hand corner Partially fibrosed and necrotic media is seen as a pale band The wall of the false aneurysm is seen in the lower left hand corner In the fibrosed and thickened adventitia of the vessel there are two calcified bacterial colonies (Hematoxylin and eosin ×40)

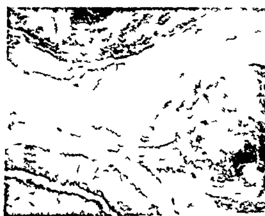


Fig 4 Section through the right common iliac artery closer to area of necrosis and rupture than in Fig 3. Thrombus overlying the thickened intima is seen above Note the extension of the intima as a necrotic band covered by the thrombus in the upper left part of the photograph A bacterial colony is seen within it The thrombus in the false aneurysmal sac and the fibrous wall of the sac is seen in the lower left part of the photograph (Hematoxylin and eosin ×160)

Examination of the abdominal aorta revealed a normal intima with a smooth and shiny appearance However the right common iliac artery was occluded by a large organizing thrombus which extended to the aortic bifurcation After removing the thrombus it was noted that the corresponding intima was roughened and granular The lumen of the vessel was enlarged Its wall was thinned and totally eroded and lost posteriorly for a short stretch before the vessel was again found to be intact distally

The left common iliac celiac, superior mesenteric and renal arteries revealed normal intimal surfaces The inferior vena cava had a normal appearance with no evidence of thrombus There was no communication with the aorta

Sections were taken from different areas of the aorta, the iliac vessels and the aneurysmal sac for histologic examination Longitudinal sections through the thrombosed right common iliac artery and its junction with the aorta revealed the transition from a vascular wall with intimal fibrosis and intact media to one with progressive attenuation of the media and marked increase in intimal thickening by smooth muscle and fibrous tissue Beyond this point and in relation to the eroded area described grossly there was attenuation of the intima with finally total disruption and necrosis of the wall (Figs 3 and 4) The thick thrombotic material covering the attenuated intima merged with the necrotic remnant of the wall and the thrombus filling the aneurysmal sac at the site of rupture Beyond the ruptured area a fibrous wall was again reconstituted which merged with the vascularized intima media of the distal portion of the common iliac artery Thick thrombus covered it on its vascular luminal aspect The clot of the aneurysmal sac was adherent to its extravascular aspect Within the necrotic and thrombotic material at the ruptured site there was a calcified bacterial colony There were two additional smaller colonies in the disrupted fibrous wall of the distal portion of the common iliac artery Brown Brenn stains revealed distinct gram positive cocci in these colonies Von Kossa stains seemed to verify the impression that the colonies were calcified Whereas the intimal thrombi and those in the aneurysmal sac were bland there were aggregates of polymorphonuclears within and about these calcified bacterial colonies The distal abdominal aorta the left common iliac artery and the distal more normal portion of the right common iliac artery were in part or in whole encased by the wall of the aneurysmal sac This wall was made up of dense fibrous tissue which fused with the adventitia of these vessels The fibrous encasement surrounded and included smal

ler thrombosed and organized blood vessels, small rather atrophic lymph nodes and nerve bundles. Toward the thrombosed surface of the sac there were patches and tracts of active granulation tissue with lymphocytes and hemosiderin-laden monocytes. Calcified bacterial colonies were found in the thrombotic material of the aneurysmal sac adjacent to the wall, in the granulation tissue, and in denser fibrous tissue of the wall of the sac. In most instances there were in relation to these colonies increased numbers of polymorphonuclears, at times amounting to microabscesses, and monocytic histiocytic cells. Since it was not suspected that the aneurysm was a mycotic one at the time of autopsy, no cultures were taken from it. However, the heart's blood was sterile.

Other blood vessels appeared normal except for the right middle cerebral artery. Its lumen was occluded 8 mm. from its origin by a thrombus measuring 3 mm. in diameter. Microscopically, the thrombus was bland and undergoing organization by a vascularized cellular fibrous tissue with light polymorphonuclear infiltration. The internal elastic lamella was destroyed, as was the media. The latter was replaced by fibrous tissue. One calcified structure was present in the fibrosed media. It was not certain whether it represented a calcified bacterial colony. The adventitia of the vessel was made up of loose fibrillar connective tissue with large numbers of hemosiderin-laden macrophages and with a small calcified mass engulfed by a foreign body giant cell.

The right hemisphere of the brain showed marked softening over an area measuring 9 by 3 cm. corresponding to the distribution of the right middle cerebral artery. In coronal sections the softened right cerebral hemisphere was in part liquefied with a thin rim of cortex beneath the pia and in part honeycombed. The globus pallidus, putamen, a small portion of the caudate nucleus, and the internal capsule were involved. The left hemisphere appeared normal.

The heart was normal in size. Both valvular and mural endocardia were free from thrombi or vegetations. There were no congenital abnormalities of the heart or great vessel.

All the other organs and systems were essentially normal except for "toxic" changes in the lymphoid follicles of the spleen and erosive changes of the lumbar vertebrae in relationship to the false aneurysm. Thick laminated clot covered the eroded areas and beneath the clot there were reactive fibrous and bony proliferative changes.

DR. KRAKOWER: Aneurysms are exceedingly uncommon in the perinatal period and in early infancy. There are little more than a dozen cases reported in the literature in the first two years of life if one excludes aneurysmal enlargement of the ductus arteriosus. The aneurysms during this age period are more apt to be either congenital or mycotic. There have been single reports of dissecting aneurysms with coarctation of the aorta in an infant of 15 days and of the ascending aorta in an infant of 9 months with Marfan's syndrome, and true aneurysms associated with giant cell arteritis and aortitis in an infant of 2 years. The mycotic aneurysm of the right common iliac artery in the present case was a false one. It is not clear from the history when the arteritis was initiated or when disruption of the vessel occurred permitting seepage of blood extraperitoneally about the aorta and the iliac vessels to give rise to the false aneurysmal sac. That the aneurysm was of longer standing was attested to by the dense fibrous capsule about it and by the erosion of the lumbar vertebrae. It is possible that the febrile disease with bronchopneumonia some 11 weeks before death may have been associated with a bacteremia and the initiation of the mycotic process. Organisms may have settled in the wall of the right middle cerebral artery to give rise to an arteritis but without aneurysmal formation. The histologic features are in keeping with a low grade arteritic process which could have been mycotic but which was greatly modified by heavy antibiotic therapy. However, owing to unforeseen circumstances, we were unable to determine whether the calcific foci in its wall had recognizable bacteria within them. Occlusive thrombosis apparently occurred some three weeks later prior to the infant's admission to the hospital for hemiplegia. As for the right common iliac artery, the mycotic process—despite antibiotic therapy—was more necrotizing but seemingly

of slow evolution Without antibiotic protection one might have expected a suppurative and necrotizing arteritis with early rupture and fatal hemorrhage As it was slow seepage of blood apparently occurred during the interval when the infant was under observation for hemiplegia and prior to admission here, some 3 weeks before death No mention of an abdominal mass was made in the original notes received from the outside hospital, but the mass was readily detected on transfer to this hospital With seepage of blood, organisms were apparently disseminated throughout the formative aneurysmal sac It may be assumed that, for a while at least they were able to grow and colonize Further growth was apparently arrested and the colonies became partly calcified and were incorporated into the organizing granulation tissue of the clot and the fibrosing wall of the aneurysmal sac

Operative manipulation and biopsies of the sac may very well have weakened the wall so that it ruptured two days postoperatively The immediate cause of death was due to intraperitoneal and retroperitoneal hemorrhage

DIAGNOSIS Mycotic arteritis of the right common iliac artery with pseudoaneurysmal formation Presumable mycotic arteritis of the right middle cerebral artery with occlusive thrombosis and extensive softening of the right cerebral hemisphere

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1 Danaraj T J and Wong H O Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal arteries and hypertension Circulation 20 856 1959

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Ventricular septal defect Clinical and hemodynamic changes in the first five years of life

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There has been considerable interest in the past decade in the natural history of isolated ventricular septal defect Spontaneous closure[1 9] progressive pulmonary vascular obstruction[7 15] right ventricular outflow tract obstruction[16 17] and aortic insufficiency[18 20] have been documented Such changes are obviously important in decisions for or against surgical intervention

To assess the likelihood of such developments a group of children with ventricular septal defects apparent since infancy have been followed now for 5 years All children were catheterized at the time of presentation to the cardiologist and 213 of 236 children considered to have adequate hemodynamic data were included in the study Thirteen of these patients on the basis of repeat catheterization and angiography have since been excluded 6 because associated lesions were discovered (2 with atrial septal defect 2 with patent ductus arteriosus one with coarctation and one with peripheral pulmonary artery stenosis) and 7 because of errors in diagnosis (3 with A V communis 2 with common ventricle one with double outlet right ventricle and 1 with Gerbode defect) This report summarizes the clinical and hemodynamic changes in the remaining 200 patients with isolated ventricular septal defects

Material and methods

Clinical examinations including chest x rays and electrocardiograms (ECG s) were performed at least once each year The timing of repeat catheterization and possible surgical intervention was at the discretion of the attending physician Sick infants not responding to medical management were recommended for pulmonary artery banding and increasing pulmonary vascular resistance was considered an indication for surgical closure of the defect

Catheterization was performed under light sedation with chlorpromazine meperidine and promethazine[21] Pressures were recorded on an Electronics for Medicine DR 8 recorder using a Stratham P23Db transducer located at one third the chest thickness below the sternum Oxygen satu

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1. Danaraj, T. J., and Wong, H. O.: Primary arteritis of abdominal aorta in children causing bilateral stenosis of renal arteries and hypertension, Circulation 20:856, 1959.
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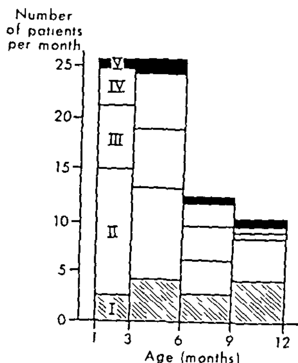


Fig 1 Histogram shows age distribution and hemodynamic group at the time of first cardiac catheterization There were no children catheterized in the first month of life The number of patients studied per month is averaged over the two or three month age period indicated The horizontal divisions denote hemodynamic groupings at the time of study

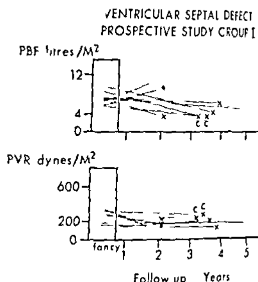


Fig 2 Group I Hemodynamic changes in 8 patients who were restudied (x = Group I defect P/S Flow Ratio <2 1 PAP <50% systemic c = spontaneous closure demonstrated angiographically)

rations and contents were assessed using a Wood oximeter and Van Slyke analysis Oxygen consumption was calculated in all instances using a figure of 180 ml per square meter per minute [2] The pulmonary artery was entered in all cases Total pulmonary vascular resistance was calculated throughout In 29 studies either the systemic oxygen saturation or the arterial pressure or both were not recorded by direct needle puncture As none of these children had elevated pulmonary artery pressure, cuff pressures were used and an arterial saturation of 95 per cent was assumed Calculations and analyses were made using conventional Fick formulas

For the sake of analysis the patients were grouped according to hemodynamic findings at the first study in infancy This grouping, which has been reported on previously,[1] is not age dependent as illustrated in Fig 1 There were 36 patients in Group I, 68 in Group II, 46 in Group III, 39 in Group IV and 11 in Group V

Group I P/S flow ratio <2 1, PA pressure <50 per cent systemic Of the 36 patients in this group, 5 were lost to follow up

One child died at 11 months of age on an Indian reservation with pneumonia The local pathologist described partial closure of the defect by fibrous tissue

The remaining 30 patients were followed for 5 years Six presented in heart failure and another 7 with cardiomegaly were digitalized All but 4 were asymptomatic by 2 years of age and digoxin was discontinued in all patients by 3 years of age Pansystolic murmurs persisted in 19 patients but the intensity of the murmur diminished and 13 patients lost their palpable thrill In 6 patients the murmur disappeared There was a significant reduction in heart size in all patients with cardiomegaly and the ECG reverted from right or combined ventricular to left ventricular hypertrophy and then to normal In 16 patients both chest x ray and ECG became normal A summary of the clinical findings in infancy and the subsequent changes is given in Table I

With this satisfactory clinical progress only 8 patients in this group had repeat catheterization The changes in pulmonary blood flow and vascular resistance are shown in Fig 2 In all but two patients there was a reduction in size of the left-to-right shunt with normal pulmonary artery pressures and P/S flow ratios of less than 1 2 1 One of these 2 patients was restudied at 26 months because of persistent cardiomegaly and combined ventricular hyper

trophy on the ECG While the pulmonary artery pressure was normal there was an increase in the size of the left to right shunt and a change in the P/S ratio from 1 5 to 2 0 1 Subsequent clinical follow up showed a diminished intensity of the murmur with loss of the thrill and reduction in heart size The abnormal ECG persisted unchanged Two patients in whom the murmur had disappeared were shown angiographically to have closed their defect spontaneously

Group II P/S flow ratio >2 1 S/P resistance ratio >7 1 There were 68 patients in this group but 6 were lost to follow up Four children died in infancy and 6 others who did not respond to medical management underwent palliative surgery The 7 patients developing right ventricular outflow tract obstruction and 2 with acquired aortic insufficiency (with similar patients in Groups III and IV) are the subject of another communication and will not be discussed in this report

Twenty seven of the remaining 43 patients improved with supervision becoming asymptomatic Twenty one were undersized with weights below the tenth percentile for age (using the Boston Children s Medical Center growth chart) and 9 had signs of heart failure Nineteen were maintained on digoxin for the first year Twenty three patients with pansystolic murmurs and thrills had large hearts with electrical evidence of combined or right ventricular hypertrophy Digoxin was stopped in 16 patients by 3 years of age All showed accelerated growth after infancy with only 4 remaining at weights below the twenty fifth percentile by 5 years of age While typical auscultatory findings persisted in most there was a reduction in heart size in all patients with large hearts initially and serial ECG s progressed to left ventricular hypertrophy and normal In 5 children the defects closed spontaneously These clinical changes are summarized in Table II Seventeen of these 27 children had repeat hemodynamic evaluations between 2 and 5 years of age All children studied showed a fall in pulmonary blood flow without alteration in vascular resistance (Fig 3) In 3 spontaneous closure was confirmed angiographically

Sixteen patients who failed to show this

Table I Ventricular septal defect Present study—Group I

Criteria	*Infancy*	*Follow up*
Auscultation		
PanSM & thrill	24	11
PanSM	4	8
Ejection SM	2	5
No murmur	0	6
X ray		
CT ratio 65 70%	5	0
60-65%	6	0
55 60%	17	12
50-55%	2	14
<50%	0	4
ECG		
RVH	5	0
CVH	17	2
LVH	6	12
Normal	2	16

Th re we 30 pati t i G o p I I f y I the t ble e th umbe f pat t w th ea h fi d g when fir t exam i d f cy d bseq tly t 5 ye r of ge Both ch ld w re rec th t ri ed
Pa Sm = p y t l c m m SM = ystol c m m CT = card th r cic RVH = right entricular hypertrophy CVH = combi d nt ic l hypert phy LVH = l ft t cula hypert phy

clinical improvement underwent surgical correction between the ages of 2 and 5 Ten were digitalized in infancy for heart failure All but 2 were below the third weight percentile for age at presentation None of these patients thrived and all but one remained below the tenth percentile (with 8 below the third percentile) at the time of surgery The abnormal clinical radiologic and electrocardiographic findings of infancy persisted in these patients until surgical intervention (Table II)

Thirteen patients were restudied prior to surgery Nine patients showed persistently high pulmonary blood flow without alteration in pulmonary vascular resistance but 4 patients showed a reduction in pulmonary blood flow with rising pulmonary vascular resistance (Fig 4) These hemodynamic changes preceded any definite clinical change and only one of the 4 patients showed pure right ventricular hypertrophy electrocardiographically

Group III P/S flow ratio >2 1 S/P resistance ratio 5 to 7 1 There were 46 patients in this group but 4 were lost to

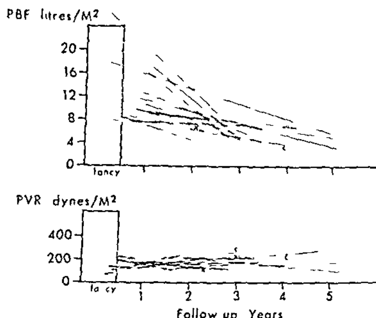


Fig 3 Group II Hemodynamic changes in 15 of the patients who improved under medical supervision (I = Group I defect c = spontaneous closure)

Table II Ventricular septal defect Present study—Group II

Criteria	Infancy	Follow up
Auscultation		
PanSM & thrill	23 (13)	18 (13)
PanSM	2 (0)	4 (0)
Ejection SM	2 (3)	0 (3)
No murmur	0 (0)	5 (0)
X ray		
CT ratio 65 70%	4 (6)	0 (4)
60 65%	8 (5)	1 (5)
55 60%	11 (5)	9 (5)
50 55%	4 (0)	12 (2)
less than 50%	0 (0)	5 (0)
ECG		
RVH	3 (4)	0 (4)
CVH	21 (11)	3 (11)
LVH	3 (0)	7 (1)
Normal	0 (1)	17 (0)

There are 43 patients in Group II in infancy 27 of whom were followed clinically for 5 years Numbers in parentheses refer to 16 children who had surgical correction The follow up examination recorded is that immediately prior to surgery
Abbreviations as in Table I

follow up Three children died in infancy and 3 others required palliative surgery Three patients developed right ventricular outflow tract obstruction and 2 acquired aortic insufficiency

Eleven of the remaining 31 patients improved clinically under supervision becoming asymptomatic by 5 years of age All but one were undersized when first seen and 5 had signs of congestive heart failure Seven patients were maintained on digoxin for the first year All had the classical auscultatory findings of a pansystolic murmur and thrill with an apical middiastolic murmur and 7 showed significantly enlarged hearts radiologically and electrical evidence of combined ventricular hypertrophy Digoxin was stopped between the ages of 2 and 4 years in 6 patients and all but 2 children had weights over the twenty fifth percentile by 5 years of age While the patients had persistent murmur and thrill all but 3 children had a reduction in heart size, and the ECGs reverted to left ventricular hypertrophy or registered normal In 2 children the defects closed spontaneously (Table III)

Ten of these 11 children had repeated hemodynamic evaluation In each patient the pulmonary blood flow fell and although 2 patients still had flow ratios greater than 2/1 their pulmonary artery pressures were normal The only children to increase pulmonary vascular resistance were the 2 shown to have an intact septum at the second study (Fig 5 A)

Six patients developed progressive pulmonary vascular obstruction Three presented in failure in infancy and 5 were undersized Three had pansystolic murmurs and thrills initially The cardiotho

racic ratios ranged from 57 to 65 per cent and all had combined ventricular hypertrophy Two patients in whom the pansystolic murmur and thrill persisted showed a significant reduction in heart size and pulmonary vascularity and ECG progression to right ventricular hypertrophy They were operated on at 2 years 4 months and 3 years 6 months without prior catheterization Studies in both one year after surgical closure showed the total pulmonary resistances to be 800 and 950 dynes per square meter respectively Another child whose parents refused surgery was cyanosed by 5 years and had only a soft ejection murmur and palpable P_2 While the heart was smaller and the vascularity reduced the ECG still showed combined ventricular hypertrophy The remaining 3 children were operated on at between 15 and 27 months on the basis of hemodynamic changes without obvious change in clinical findings except a slight reduction in the heart size radiologically

Fourteen patients had persistence of their large defects and because of symptoms 13 had surgical corrections between the ages of 15 months and 4 years Seven patients presented in heart failure and 9 had initial weights below the third percentile There was little or no change in the clinical radiologic or electrocardiographic findings up to the time of surgery except that 4 children with short murmurs initially developed the typical pansystolic murmur and thrill and one child showed an ECG change from combined to left ventricular hypertrophy (Table III)

Thirteen of these patients were restudied before surgery Five showed some reduction in pulmonary blood flow with a slight rise in vascular resistance In the other patients the findings did not change (Fig 5 B)

Group IV P/S flow ratio >2 1 S/P resistance ratio <5 1 Of 39 children in this group 7 were lost to follow up 4 died and 5 required palliative surgery in infancy Three children developed infundibular obstruction and one acquired aortic insufficiency

Seven of the remaining 24 patients became asymptomatic in the first 5 years of life Initially all had body weights below the tenth percentile for age with 5 below the third percentile Four children pre

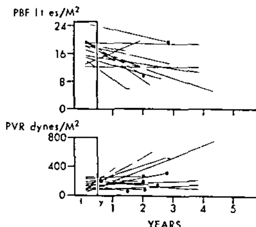


Fig 4 Group II Changes in pulmonary blood flow and vascular resistance in 13 of the patients who underwent surgical correction. (● = Group II defect P/S Flow Ratio >2 1 S/P Resistance Ratio >7 1 □ = Group IV defect P/S Flow Ratio >2 1 S/P Resistance Ratio <5 1)

Table III Ventricular septal defect Present study—Group III

Criteria	*Infancy*	*Follow up*
Auscultation		
PanSM & thrill	11 (11)	6 (12)
PanSM	0 (4)	2 (3)
Ejection SM	0 (5)	1 (5)
No murmur	0 (0)	2 (0)
X ray		
CT ratio 65 70%	2 (6)	0 (0)
60 65%	5 (9)	3 (9)
55 60%	3 (4)	4 (8)
50-55%	1 (1)	3 (3)
less than 50%	0 (0)	1 (0)
ECG		
RVH	1 (2)	0 (4)
CVH	7 (18)	0 (15)
LVH	3 (0)	6 (1)
Normal	0 (0)	5 (0)

Th re 31 pat ents in G p III in i f cy 11 of whom w f llowed clinically for 5 yea s. Figure par these f r t th se child operated o bef th g f 5 yea s. Th f ll w p examinatio l that mmed t ly pri r to surg ry
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sented in heart failure and 2 others were digitalized in the first year The auscultatory findings in 6 were classical Radiologically heart sizes were greater than 59 per cent of the transthoracic diameter in all patients and 6 had biventricular hypertrophy By 5 years all showed accelerated growth While the pansystolic murmur and

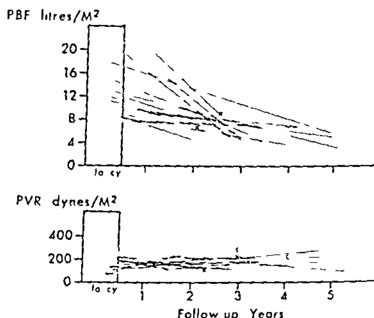


Fig 3 Group II Hemodynamic changes in 15 of the patients who improved under medical supervision (x = Group I defect c = spontaneous closure)

Table II Ventricular septal defect Present study—Group II

Criteria	Infancy	Follow up
Auscultation		
PanSM & thrill	23 (13)	18 (13)
PanSM	2 (0)	4 (0)
Ejection SM	2 (3)	0 (3)
No murmur	0 (0)	5 (0)
X ray		
CT ratio 65 70%	4 (6)	0 (4)
60 65%	8 (5)	1 (5)
55 60%	11 (5)	9 (5)
50 55%	4 (0)	12 (2)
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ECG		
RVH	3 (4)	0 (4)
CVH	21 (11)	3 (11)
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Normal	0 (1)	17 (0)

There are 43 patients in Group II in infancy 27 of whom were followed clinically for 5 years Numbers in parentheses refer to 16 children who had surgical correction The follow up examination recorded is that immediately prior to surgery
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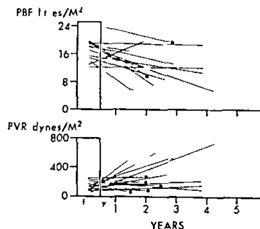


Fig 4 Group II Changes in pulmonary blood flow and vascular resistance in 13 of the patients who underwent surgical correction (● = Group II defect P/S Flow Ratio >2 1 S/P Resistance Ratio >7 1 □ = Group IV defect P/S Flow Ratio >2 1 S/P Resistance Ratio <5 1)

Table III Ventricular septal defect Present study—Group III

Criteria	*Infancy*	*Follow up*
Auscultation		
PanSM & thrill	11 (11)	6 (12)
PanSM	0 (4)	2 (3)
Ejection SM	0 (5)	1 (5)
No murmur	0 (0)	2 (0)
X ray		
CT ratio 65 70%	2 (6)	0 (0)
60-65%	5 (9)	3 (9)
55 60%	3 (4)	4 (8)
50-55%	1 (1)	3 (3)
less than 50%	0 (0)	1 (0)
ECG		
RVH	1 (2)	0 (4)
CVH	7 (18)	0 (15)
LVH	3 (0)	6 (1)
Normal	0 (0)	5 (0)

Th re are 31 p tie t in G p III in infancy 11 of whom were f llowed l cally fo 5 ye s F gu es i p th se f t th se child perated n bef th g f 5 y s. Th f llow p exam nat n i that mm d t ly pri t surgery
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sented in heart failure and 2 others were digitalized in the first year The auscultatory findings in 6 were classical Radiologically heart sizes were greater than 59 per cent of the transthoracic diameter in all patients and 6 had biventricular hypertrophy By 5 years all showed accelerated growth While the pansystolic murmur and

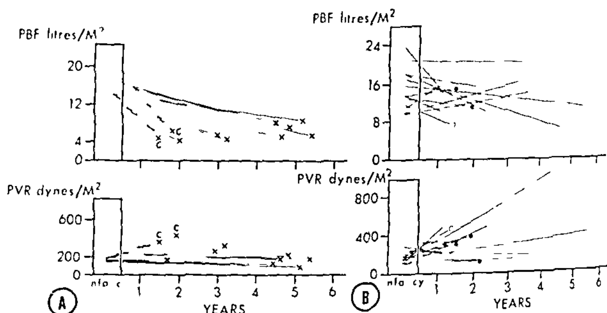


Fig. 5 A and B Group III A The fall in pulmonary blood flow recorded in 10 patients who improved clinically while under supervision (x = Group I defect c = spontaneous closure) B Changes in pulmonary blood flow and vascular resistance in 12 patients prior to surgical correction Permission for surgery had been refused in the one child with severe pulmonary vascular obstruction ● = Group II defect □ = Group IV defect)

Table IV Ventricular septal defect Present study—Group IV

Criteria	*Infancy*	*Follow up*
Auscultation		
PanSM & thrill	6 (14)	4 (13)
PanSM	0 (0)	0 (0)
Ejection SM	1 (3)	1 (3)
No murmur	0 (0)	2 (1)
X ray		
CT ratio 65 70%	2 (3)	0 (3)
60 65%	4 (10)	0 (8)
55 60%	1 (4)	3 (5)
50 55%	0 (0)	4 (1)
ECG		
RVH	1 (3)	0 (7)
CVH	6 (14)	1 (10)
LVH	0 (0)	2 (0)
Normal	0 (0)	4 (0)

There are 24 patients in Group IV in infancy 7 of whom were followed clinically for 5 years Figures in parentheses refer to findings in children submitted for surgical correction before the age of 5 years The following findings are those recorded immediately before surgery

Abbreviations as in Table I

thrill persisted in 4 children all showed a reduction in the heart size and ECG changes to either left ventricular hypertrophy or normal (Table IV) In 2 children the defect closed spontaneously

In 5 of these patients, repeat cardiac catheterization was performed In 2 patients there was a significant reduction in total pulmonary vascular resistance associated with spontaneous closure (Fig 6 A)

Six children developed progressive pulmonary vascular obstruction When first seen all had weights below the third percentile and 4 were in heart failure Five had pansystolic murmurs and thrills All had enlarged hearts with increased vascular markings radiologically Three children had right ventricular hypertrophy on their initial ECG (Table IV) In one child in whom surgery was refused the shunt was reversed by 5 years of age Clinically she was cyanosed and she had a palpable right ventricular heave and loud pulmonary component of the second heart sound without a murmur Radiologically her heart was small the right ventricle and main pulmonary artery were enlarged and the pulmonary vessels showed peripheral 'cut off' One child in whom the murmur became soft and short in association with a loud P_2 and a reduction in heart size had surgical closure at 2 years without further investigation The postoperative recovery was uneventful but at a study 8 months later the total pulmonary vascular resistance was 1 140 dynes per square meter She died 4 years later with severe pulmonary vascular disease The other 4 children had surgical correction between 18 and 36

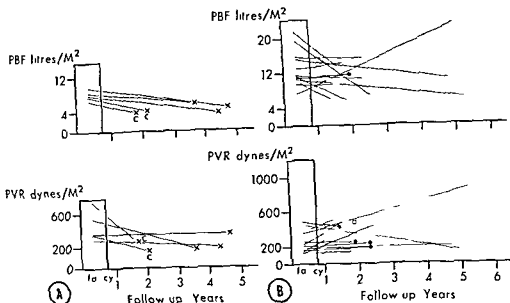


Fig 6 *A* and *B* Group IV 1 Hemodynamic findings in 5 of 7 patients who improved clinically while under supervision (x = Group I defect c = spontaneous closure) *B* Hemodynamic findings in 12 patient 11 of whom had surgical corrections attempted (● = Group II defect □ = Group IV defect.)

months on the basis of hemodynamic changes without obvious change in the clinical parameters (Fig 6 *B*)

Eleven children had persistent large defects and because of symptoms 9 had surgical closure between the ages of 2 and 4 years All but one child had weights below the third percentile at initial examination Five presented in heart failure All but two had pansystolic murmurs associated with a thrill Cardiomegaly with pulmonary plethora was seen radiologically without exception as was combined ventricular hypertrophy This clinical picture persisted unchanged until surgical intervention although in 3 patients the ECG progressed from a combined pattern to right ventricular hypertrophy (Table IV)

Seven of these children had repeat hemodynamic evaluation In one instance there was a dramatic increase in flow associated with a fall in pulmonary vascular resistance The other 6 children had a persistent high flow without change in resistance (Fig 6 *B*)

Group V P S flow ratio <2 1 PA pressure >50 per cent systemic Of the 11 patients in this group one child died in heart failure at 2 months and another died during surgical correction at 7 months A third child underwent surgical closure at 2½ years

Five of the remaining 8 children presented with heart failure and all received digoxin All had a harsh pansystolic murmur associated with a thrill The chest x ray showed a cardiothoracic ratio greater than 60 per cent in 6 patients and all had abnormal ECG s (Table V)

Marked clinical improvement was noted in 4 patients on follow up They were asymptomatic after the first year and stopped digoxin by the end of the second year The heart size returned to normal as did the ECG While 2 still have pansystolic murmurs and the associated thrill the absence of a murmur in the other two suggests spontaneous closure—in one this has been proved by catheterization

While the remaining 4 children are relatively asymptomatic growth has been retarded (3 are in the tenth percentile) the murmurs persist and the hearts are enlarged and hyperactive Cardiac catheterization demonstrated in each an increase in the left to right shunt with flow ratios ranging from 2 2 to 3 1 1 Pulmonary pressures have however fallen to normal levels and there is a reduction in pulmonary vascular resistance (Fig 7)

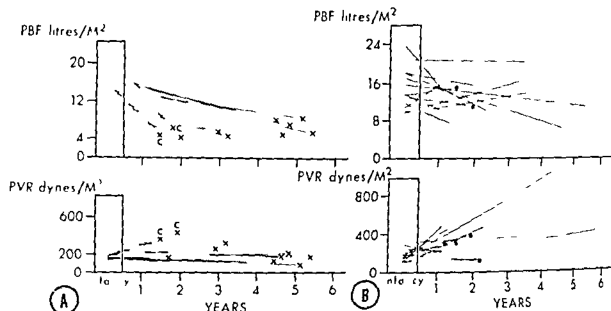


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Table IV Ventricular septal defect Present study—Group II

Criteria	Infancy	Follow up
Auscultation		
PanSM & thrill	6 (14)	4 (13)
PanSM	0 (0)	0 (0)
Ejection SM	1 (3)	1 (3)
No murmur	0 (0)	2 (1)
X ray		
CT ratio 65 70%	2 (3)	0 (3)
60 65%	4 (10)	0 (8)
55 60%	1 (4)	3 (5)
50 55%	0 (0)	4 (1)
ECG		
RVH	1 (3)	0 (7)
CVH	6 (14)	1 (10)
LVH	0 (0)	2 (0)
Normal	0 (0)	4 (0)

There are 24 patients in Group IV in infancy 7 of whom were followed clinically for 5 year Figures in parentheses refer to findings in children submitted for surgical correction before the age of 5 years The follow up findings are those recorded immediately before surgery

Abbreviations as in Table I

thrill persisted in 4 children all showed a reduction in the heart size and ECG changes to either left ventricular hypertrophy or normal (Table IV) In 2 children the defect closed spontaneously

In 5 of these patients, repeat cardiac catheterization was performed In 2 patients there was a significant reduction in total pulmonary vascular resistance associated with spontaneous closure (Fig 6 A)

Six children developed progressive pulmonary vascular obstruction When first seen all had weights below the third percentile and 4 were in heart failure Five had pansystolic murmurs and thrills All had enlarged hearts with increased vascular markings radiologically Three children had right ventricular hypertrophy on their initial ECG (Table IV) In one child in whom surgery was refused the shunt was reversed by 5 years of age Clinically she was cyanosed and she had a palpable right ventricular heave and loud pulmonary component of the second heart sound without a murmur Radiologically her heart was small the right ventricle and main pulmonary artery were enlarged and the pulmonary vessels showed peripheral 'cut off' One child in whom the murmur became soft and short in association with a loud P_2 and a reduction in heart size had surgical closure at 2 years without further investigation The postoperative recovery was uneventful but at a study 8 months later the total pulmonary vascular resistance was 1 140 dynes per square meter She died 4 years later with severe pulmonary vascular disease The other 4 children had surgical correction between 18 and 36

but these children with persistent small defects have normal hearts functionally radiologically and electrocardiographically with little increase in pulmonary blood flow The clinical course is that of a maladie de Roger defect [3]

There were 14 children with pulmonary vascular resistances greater than 400 dynes initially This finding was not restricted to the very young as 6 of the children were over 6 months of age at the time of study The flow ratio was less than 2 to 1 in 11 patients and while the remaining 3 were assigned to Group IV on the basis of flow ratio absolute values for pulmonary blood flow in each was less than 8 L per minute per square meter In these children the size of the defect was not reflected by the pulmonary blood flow as is illustrated by later findings in 12 patients With a fall in resistance after infancy 6 showed increased pulmonary blood flow indicative of a large defect while 6 had small defects 3 of which closed While the mechanism for the initially high pulmonary vascular resistance is not known it could result from delayed resolution of the fetal vascular pattern in the lung As none of the 6 patients with persistent large defects developed arteriolar damage it is possible that delayed resolution of this fetal vascular pattern occasionally protects these patients from the Eisenmenger reaction The smaller number of patients in this group prevents a definite conclusion Further observation is necessary to understand one patient whose defect closed spontaneously yet at 5 years of age had a pulmonary vascular resistance of 580 dynes per square meter

Infants with a flow ratio greater than 2 to 1 have a variable natural evolution Some die in infancy while others tend to close their defects the majority however have persistence of their large defect and may develop the Eisenmenger reaction [4] of progressive pulmonary arteriolar obstruction The actual mortality rate in these children was 7 per cent but as palliative surgery was undertaken only in an emergency when medical treatment failed to control heart failure as many as 16 per cent may be at risk of dying in the first year of life

Approximately 45 per cent of the children survived infancy without surgery and

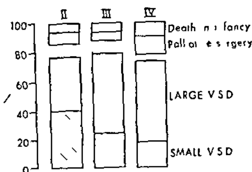


Fig 9 The mortality rate and incidence of palliative surgery in infancy in those children who initially had flow ratios greater than 2 to 1 The shaded area represents those children who had a reduction in size of the defect. The interrupted lines indicate children with incomplete follow up

had regular assessments and repeat catheterization The proportion of these children who reduced the size of their defect varied from 50 per cent in Group II to 25 per cent in Group IV (Fig 9) Of the 45 children who underwent this change 9 had completely closed defects This incidence of 20 per cent spontaneous closure in those children who decrease the size of their defect is independent of hemodynamic grouping and very similar to the incidence of spontaneous closure in children who initially have a small or restrictive ventricular septal defect

The large defect persisted in 70 patients 60 per cent of those with a flow ratio greater than 2 to 1 who survived infancy without surgery This finding was proportionally more frequent in Group IV than in Group II (Fig 9) While half of these children had no clinical or hemodynamic change up to the time of surgery 22 per cent had an elevation in pulmonary vascular resistance indicative of the Eisenmenger reaction and 19 per cent developed gradients at the right ventricular level suggesting progressive obstruction to flow across the right ventricular outflow tract

Comparison of those patients with persistent large defects who do not damage their pulmonary arterioles with those who do may help elucidate the precipitating factors in the Eisenmenger reaction Certainly all children who develop progressive pulmonary arteriolar disease have low resistance and excessive pulmonary blood flow in infancy but not all children with

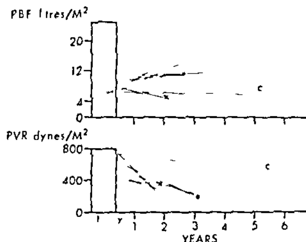


Fig. 7 Group V Six of the 8 patients in this group followed for 5 years had repeat heart catheterization. In 4 patients the fall in pulmonary vascular resistance (*PVR*) was associated with increased flow. *PBF* = pulmonary blood flow.

Table V Ventricular septal defect Present study—Group V

Criteria	*Infancy*	*Follow up*
Auscultation		
PanSM & thrill	8	5
PanSM	0	1
No murmur	0	2
X ray		
CT ratio 60 65%	6	1
55 60%	2	5
50 55%	0	2
ECG		
RVH	3	0
CVH	5	3
LVH	0	1
Normal	0	4

There are 8 patients in Group V in infancy. This table is a summary of findings when first examined in infancy and subsequently at 5 years of age.
Abbreviations as in Table I.

Discussion

The children analyzed in this report were selected because of symptoms for cardiac assessment in the first year of life. Such selection precludes discussion of the natural history of this condition, but the results of such a study are of practical value to physicians who treat children with congenital heart disease. Comparison of the incidence of hemodynamic groups in 120 children from this study (called "prospective study" in Fig. 8), who survived infancy without surgery and who neither closed their defects spontaneously nor developed infundibular stenosis, with 223 children over the age of 2 in a previous study[1] (called "retrospective study" in Fig. 8) does suggest that the infants in this study reflect the clinical spectrum normally seen in this condition. The lower incidence of Group V patients can be explained by the early surgery and younger age in this study.

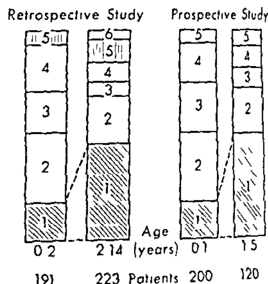


Fig. 8 The hemodynamic groups in 414 children with isolated ventricular septal defects catheterized between 1955 and 1964 compared with 200 infants in this prospective study. The 120 children in the 1 to 5 year age group are those children who survived infancy without surgery excluding those with spontaneous closure or acquired infundibular stenosis.

The children in Group I tend to have smaller hearts and a lower incidence of heart failure (20 per cent) than those in other groups, but initial physical findings did not facilitate classification of individual patients. There are changes, however, on subsequent examinations which suggest a good prognosis. In particular accelerated growth, a reduction in heart size, or an electrocardiographic evolution to left ventricular hypertrophy correlate with a reduction in the size of the defect. Assessment of ultimate prognosis is facilitated by grouping the infants on the basis of pulmonary to systemic flow ratio. The patients in Group I had relatively small defects restricting the size of the left to right shunt. There was a further reduction in the size of these defects and a 20 per cent incidence of spontaneous closure in the first 5 years of life. Further follow up is necessary to determine the ultimate incidence of closure

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these early findings develop this change. It was not possible to separate those with a reactive pulmonary vascular bed on the basis of clinical or hemodynamic findings in infancy. Subsequent clinical changes tended to follow rather than precede the early rise in vascular resistance, and it is felt that only repeat hemodynamic evaluation by 12 to 15 months of age will identify such children at a time when corrective surgery may prevent progression of the vascular lesion. A more detailed comparison of these children will be presented later.

Summary

Two hundred consecutive infants with isolated ventricular septal defects were assessed clinically and hemodynamically and then followed throughout the first 5 years of life. Those infants who had flow ratios less than 2 to 1 generally became asymptomatic because of diminution in size of the defect. Complete closure occurred spontaneously in 20 per cent.

The majority of infants had flow ratios greater than 2:1 and in these the natural evolution varied. At least 15 per cent of these infants may die from their cardiac lesion in infancy. However, approximately 40 per cent of those who survive will have closed defects and 20 per cent of those who show this reduction in size will have spontaneously closed defects by 5 years of age. Those children in whom the large defect persists remain symptomatic and fail to thrive. There is little or no change in clinical, radiologic, or electrocardiographic findings up to the time of surgery, but hemodynamic reassessment indicates that at least 20 per cent of such children may develop progressive pulmonary arteriolar disease and that such changes, when they are going to occur, will be evident hemodynamically in the second year of life.

When all the children with flow ratios greater than 2 to 1 are considered, the mortality rate was 7 per cent, 9 per cent required palliative surgery in infancy, 6 per cent underwent spontaneous closure, and 10 per cent developed the Eisenmenger reaction.

The authors wish to express their appreciation to Drs. Fowler, Braudo, and Disenhouse, members of the department who allowed their patients to be included in this study. Many of the pediatricians on the hospital staff referred patients for assessment. Residents and fellows working in the department during the 7 year period of the study assisted in clinical and hemodynamic evaluations. The comparability of the hemodynamic data attests to the high standards maintained in the laboratory by nurses under supervision of Mrs. Janiss. The analysis was made easy by an efficient record room staff under the direction of Miss McLaughlin.

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on propranolol given 160 mg daily for 4 weeks compared to placebo

However if one applies to Gianelly and associates data the criterion of a 50 per cent or greater reduction of anginal episodes as a measure of significant response in angina one finds that only 7 of their 19 patients (37 per cent) had significantly less angina on propranolol compared to placebo[10] and that 2 of their 19 patients (11 per cent) had significantly more angina on propranolol compared to placebo [10] One of their 7 patients who significantly improved on propranolol had experienced only 9 anginal episodes in a 4 week period or 2¼ anginal episodes per week on placebo and a second patient who significantly improved on propranolol had experienced only 10 anginal episodes in a 4 week period or 2½ anginal episodes per week on placebo I would not treat either of these two patients with propranolol because their angina was too mild That leaves only 5 of 19 patients (26 per cent) benefiting subjectively from propranolol Finally if one takes the patient who had experienced the greatest relief of angina from propranolol one finds that this patient had shown a better exercise performance on placebo [10]

If one analyzes the exercise data reported by Gianelly and his associates [5] one finds that only 5 of their 19 patients (26 per cent) had shown an improved exercise performance of 25 per cent or *greater on* propranolol compared to placebo whereas 2 of their 19 *patients* (11 per cent) had *exhibited greater than a 25 per cent de*crease in exercise performance on propranolol compared to *placebo Gianelly* and his associates[5] were also the first investigators to point out that propranolol allowed some patients to do *more exercise* while their ST segments were depressed and they raised the following question The significance of this consequence of propranolol administration is difficult to assess *Is it* harmful for a patient with angina *pectoris* to exercise in the face of ST segment depression? Their electrocardiographic (ECG) observations have been confirmed by other investigators [1,9,11] Because propranolol causes an increase in coronary vascular resistance an increase in heart size and volume and a reduction in coronary blood flow Gianelly and his associates[5] also wondered whether the relief of pain of angina is not counterbalanced by effects that may in the long run be harmful

Proctor and colleagues[1] pointed out that Sandler and co workers[8] had reported that propranolol 300 mg daily was effective in reducing anginal attacks and nitroglycerin consumption because they had compared the results of propranolol therapy with the control period instead of with the placebo period By statistically analyzing Sandler and associates [8] data Proctor and co workers[1] demonstrated that propranolol 300 mg daily compared to placebo was no more effective than placebo in reducing either anginal attacks or nitroglycerin consumption

If one analyzes the data reported by Battock and co workers [9] one finds that only 4 of their 12 patients (33 per cent) had shown a +2 or greater subjective and objective improvement on propranolol compared to placebo These investigators[9] also demonstrated that at similar pressure rate indices after exercise ST segment depression was actually greater in patients on propranolol compared to placebo

We[13] found in a double blind study involving 24 patients with *angina pectoris* due to coronary artery disease that propranolol 40 mg alone or in combination with oral isosorbide dinitrate did not significantly *affect* the response of the entire group of patients to exercise induced angina in comparison with placebo We[12] also *reported our data from a double blind* crossover study involving 23 patients with angina pectoris due to coronary artery disease who received propranolol 160 mg daily plus sublingual isosorbide dinitrate administered 5 mg 4 times daily for six weeks and an oral plus a sublingual placebo *given 4 times* daily for six weeks Three of our 23 patients (13 per cent) were unable to tolerate the combination of propranolol *plus* isosorbide dinitrate Three of our 23 patients (13 per cent) had experienced a similar number of anginal attacks requiring *nitroglycerin* on the drug combination as *on the* placebos Seven of our 23 patients (30 per cent) had significantly fewer anginal attacks requiring nitroglycerin on *the drug* combination compared to the placebos Ten of our 23 patients (44 per

The medical treatment of angina pectoris VI. Propranolol as an antianginal drug

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Propranolol has pharmacologic actions which may either improve or worsen angina pectoris Beneficial effects include lowering of the systolic arterial pressure after exercise This decrease coupled with the negative chronotropic effect produced by propranolol diminishes the tension time index reducing myocardial oxygen consumption Propranolol also reduces the myocardial oxygen demand by decreasing the velocity of myocardial fiber contraction

The harmful effects of propranolol in angina pectoris include prolongation of the systolic ejection period This action raises the tension time index, increasing myocardial oxygen consumption Propranolol causes a higher left ventricular end diastolic pressure at rest and during exercise in most patients despite diminished or unchanged stroke work Myocardial contractility is depressed at rest and during exercise We[1,2] reported that propranolol precipitated overt congestive failure in 3 of 23 patients (13 per cent) with angina pectoris due to coronary artery disease and Zeft and his associates[3] reported that propranolol precipitated overt congestive failure in 6 of 65 patients (9 2 per cent) with angina pectoris due to coronary artery disease Propranolol lowers the stroke index and cardiac index Propranolol causes ventricular dilatation at rest and after exercise By Laplace's law this increase in size of the ventricular chamber increases the ventricular wall tension and, consequently, myocardial oxygen demand Propranolol causes an increased coronary vascular resistance, a decreased coronary blood flow and a widened A V oxygen difference Propranolol also blocks the coronary artery vasodilator response to beta adrenergic stimulation and causes unmasking of alpha receptor coronary vasoconstriction

Therefore the physiologic data suggest that propranolol might either relieve or aggravate angina pectoris In the study reported by Robin and his associates[4] the net result was an impairment of myocardial cellular oxidation with a negative reduction oxidation potential or an anaerobic metabolic response

Propranolol has been reported to be very effective as an antianginal drug by many investigators[3,5,9] Gianelly and his associates[5] stated that 17 of 19 patients (89 per cent) with angina pectoris due to coronary artery disease had fewer episodes of angina

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this time supporting the safety and efficacy of propranolol for general use as an anti anginal drug

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cent) had significantly fewer anginal attacks requiring nitroglycerin on the placebos compared to the drug combination.

Two of our 20 patients (10 per cent) had a significant improvement in exercise performance on propranolol plus sublingual isosorbide dinitrate compared to the oral plus sublingual placebos.[1] Eight of our 20 patients (40 per cent) had a significant decrease in exercise performance on the drug combination compared to the placebos. There was no significant difference in exercise performance in 10 of our 20 patients (50 per cent) whether the patients were on the drug combination or on the placebos. Sixty-one per cent of the exercise ECG's were abnormal on the placebos and 64 per cent of the exercise ECG's were abnormal on propranolol plus sublingual isosorbide dinitrate.[1]

Goldbarg and his associates[11] reported that propranolol 160 mg. daily alone, or in combination with oral isosorbide dinitrate given for one month periods, was effective in reducing the frequency of anginal pains in comparison with placebo but did not significantly improve exercise performance nor prevent ischemic changes in the exercise ECG in a group of 21 patients with angina pectoris due to coronary artery disease.

Zeft and his associates[3] found that 8 of their 65 patients (12.3 per cent) with angina pectoris due to coronary artery disease died during their study period on propranolol. This mortality figure was interpreted[3] to imply that propranolol neither improved survival nor altered the natural history of severe coronary artery disease. Zeft and his associates[3] also stated that beneficial effects in angina pectoris from propranolol are obtained often only with doses far in excess of those which produce hemodynamic effects of beta sympathetic blockade. These investigators wondered whether the efficacy of propranolol in angina pectoris was related more to known anesthetic properties than to actual beta adrenergic receptor blockade. If their hypothesis is correct, one also wonders whether propranolol removes the desirable warning signal of angina pectoris.

Sandler and Clayton[14] reported that there was no significant difference in the number of circuits of exercise completed on propranolol 320 mg. daily compared to placebo. Nine of their 15 patients (60 per cent) with angina pectoris due to coronary artery disease developed angina during their exercise test on propranolol compared to 8 of their 15 patients (53 per cent) on placebo.[14] Propranolol did not significantly reduce the amount of ST segment depression or the duration of ST segment depression during or after exercise in their patients in comparison with placebo.

Sandler and Clayton[14] found that the mean number of anginal attacks was 8.3 per week on placebo and 5.8 per week on propranolol. However, the number of nitroglycerin tablets consumed was 25.3 per week on placebo and 41.9 per week on propranolol. Therefore, by simple calculation, the number of nitroglycerin tablets consumed per anginal attack in their patients was 3.0 on placebo and 7.2 on propranolol.

We feel that propranolol should not be used as an antianginal drug in patients with mild angina pectoris or in patients with congestive failure, a recent myocardial infarction, poor myocardial contractility, significant aortic or mitral valvular disease, sinus bradycardia, greater than first degree A-V block, severe regional vascular insufficiency, chronic obstructive lung disease, a history of bronchial asthma, or with allergic rhinitis during the pollen season. Propranolol should also be avoided in patients who are receiving adrenergic-augmenting psychotropic drugs or in patients prone to develop hypoglycemia.

Propranolol may be of dramatic help to some patients with severe angina pectoris but may also be harmful to other patients. Therefore, we advocate that patients receiving propranolol for severe angina pectoris should have exercise performance studies and exercise ECG's before and during treatment. If the exercise performance deteriorates on propranolol or if the exercise ECG reveals increased ischemic ST segment depression on propranolol, this drug should then be discontinued and the clinical situation re-evaluated. Finally, on the basis of the available data, the Food and Drug Administration and an Advisory Scientific Committee to the Food and Drug Administration felt that there was inadequate information at

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Propranolol may be of dramatic help to some patients with severe angina pectoris but may also be harmful to other patients. Therefore, we advocate that patients receiving propranolol for severe angina pectoris should have exercise performance studies and exercise ECG's before and during treatment. If the exercise performance deteriorates on propranolol or if the exercise ECG reveals increased ischemic ST segment depression on propranolol, this drug should then be discontinued and the clinical situation re-evaluated. Finally, on the basis of the available data, the Food and Drug Administration and an Advisory Scientific Committee to the Food and Drug Administration felt that there was inadequate information at

treatment of hypertension angina pectoris heart failure and arrhythmias in patients with asthma. Sympathomimetic drugs used in the treatment of bronchospasm may be contraindicated in patients with cardiovascular diseases. This may make optimal therapy difficult in patients who have asthma combined with cardiovascular disease. In many cardiovascular diseases a β adrenergic blocking agent may be the drug of choice. However as the most commonly used β blocking agents (propranolol alprenolol) can induce bronchospasm due to blockade of β-adrenergic receptors in the bronchial muscles as well as in the heart they cannot be used in patients with bronchial asthma.

Sympathomimetic amines such as ephedrine and epinephrine (adrenaline) stimulate both α and β adrenergic receptors resulting in relaxation of the bronchial muscles but also in vasoconstriction tachycardia and increased systemic blood pressure. Isoprenaline and orciprenaline stimulate only the β adrenergic receptors. However β-stimulation causes such side-effects as palpitations and tachycardia and might even induce a fatal arrhythmia. The tachyarrhythmias often seen during severe bronchospasm are dangerous: the circulation already is disturbed by the airway obstruction which causes reduced venous return and variation of stroke volume during the respiratory cycle.[3] The combination of disturbed hemodynamics hypoxemia respiratory alkalosis or acidosis and a high endogenous and/or exogenous sympathetic stimulation adds up to a high risk of fatal arrhythmia.

Recently new drugs have become available which will be of benefit in the treatment of patients who have the combination of bronchial asthma and cardiovascular disease. Two new drugs terbutaline (Bricanyl) and salbutamol (Ventolin) which selectively stimulate the bronchial β_2-adrenergic receptors are available. These drugs have marked bronchodilating effects of prolonged duration with little or no effect in therapeutic dosage on the heart. The stimulation of β_2-adrenergic receptors in the peripheral vessels will result in vasodilatation and reduced peripheral resistance. Several studies reported from this and other clinics have shown that terbutaline has a pronounced long-lasting bronchodilating effect with negligible circulatory effects in the doses used.[4]

The new β adrenergic blocking agent practolol (Eraldin) is claimed to selectively block the β receptors (in the heart) and thus theoretically would be useful in the treatment of tachyarrhythmias in patients with bronchospasm. In recommended doses the new β blocker has little or no effect on the bronchial β_2 receptors.[5] The results of treatment of various arrhythmias in asthmatics with combinations of β_2-stimulation and β blockade are given in this pilot study.

The study was made on 23 patients with bronchial asthma of varying severity and a mean age of 65 years (50 to 74 years). All patients were well known at the clinic and all were receiving chronic antasthmatic treatment. They were all hospitalized for severe asthma and the treatment was started and followed up at the hospital. Three of them had prolonged therapy-resistant status asthmaticus and circulatory insufficiency. 12 had supraventricular tachycardia with frequent supraventricular extrasystoles or ventricular extrasystoles, six had atrial fibrillation and one severely decompensated woman had ventricular tachycardia. One patient had Wolff-Parkinson-White (WPW) syndrome with frequent daily attacks of tachycardia. Three patients had supraventricular extrasystoles without tachycardia.

All patients were given practolol by mouth usually 100 mg twice daily. In seven patients the treatment was started with practolol given intravenously in a dose of 10 mg during a 5 minute period. Three of these patients were in severe status asthmaticus. During the injection the electrocardiogram (ECG) was recorded each minute. As a rule the patients were checked by daily ECG recording and lung auscultation. In seven patients blood pressure measurements were performed twice daily during the treatment as well as 3 to 5 days before. The severity of the bronchial asthma was judged according to the clinical condition. Practolol was not given unless the patient was receiving maximal β_2-stimulation from 5 mg of terbutaline 3 to 4 times daily.

In all patients the practolol treatment could be continued without any sign of impairment of their bronchial asthma. The therapeutic result of the treatment was good. All twelve patients with supraventricular tachycardia combined with supraventricular extrasystoles returned to sinus rhythm and the average heart rate was reduced from 125 to 78 beats per minute. In seven of these patients the blood pressure was reduced from 166/88 to 137/76 mm Hg. Atrial fibrillation was treated in six patients: three of these returned to normal sinus rhythm by practolol, in two the arrhythmia was converted to sinus rhythm by countershock and in one by a combination of practolol and quinidine. All six had been previously digitalized. One patient with ventricular tachycardia which could not be controlled by intravenous infusion of lidocaine was converted to normal sinus rhythm after 100 mg of practolol given orally.

Practolol has not been previously given to asthmatics for treatment of concomitant cardiovascular disorder. However practolol has been given as a single dose to patients with asthma without or with only moderate symptoms in order to ascertain whether there is any β_2-blocking effect of practolol.[5] It has been shown that practolol without administration of isoprenaline gave a transitory reduction of $FEV_{1.0}$ which could be prevented by isoprenaline premedication.[6] Furthermore one patient with asthma and hypertension has been treated with practolol without impairment of the asthmatic condition.[7] Practolol has been found to prevent isoprenaline-induced tachycardia without impairment of the bronchodilating effect.

Practolol has thus been shown to be a selective blocking agent mainly acting on the β_1 adrenergic receptors with minimal effect on the β_2-adrenergic receptors when given in the recommended doses. Our experience of practolol is that this cardioselective β-adrenergic blocker in contrast to conventional β-adrenergic blockers could be given to patients with bronchial asthma with cardiovascular diseases in which a β blocker is indicated. As practolol how

Annotations

A sphygmomanometer in every home

Hypertension continues to be one of the most important and most common causes of disease and death in man in spite of the fact that hypertension is amenable to treatment Successful treatment is readily achieved if hypertension is recognized early treatment instituted early and dangerously high levels of blood pressure prevented Unfortunately many patients do not seek advice for hypertension until symptoms and/or signs appear and frequently not until symptoms are severe Too often, serious and irreversible cardiovascular and renal damage has already occurred before the hypertension is treated Furthermore patients who have recovered from diseases associated with hypertensive states such as acute glomerulonephritis toxemia of pregnancy psychogenic stress and the like are discharged and not followed properly by a physician These patients gradually develop abnormally high levels of blood pressure and associated symptoms or complications before the hypertension is again detected Frequently it may be a stroke with eventual death that causes the patient to consult a physician With occasional recording of blood pressure at home hypertensive levels can be detected early and a physician consulted before the hypertension becomes irreversible Furthermore it is impossible to manage hypertension properly without home recording of blood pressure at frequent intervals of time even though effective antihypertensive drugs are available It is no more possible to regulate blood pressure medicine elegantly for a patient with hypertension without home recording of blood pressure than it is to regulate the dose of insulin for a patient with diabetes mellitus without testing his urine for glucose at home

Every home should have a reliable sphygmomanometer and one or more members of the family should be taught to record periodically blood pressures of members of the family in association with various environmental circumstances and activit A person s blood pressure should be checked if he experiences headaches blurred vision giddiness or any other symptoms of ill health or after any psychic or physical stress This practice may appear absurd to many physicians but if one reviews the medical literature of the late years of the last century he will find that physicians at that time wrote about the importance of the clinical thermometer They often stated that the clinical thermometer was an extremely complex important and sensitive scientific device which should be entrusted to physicians only and not to nurses or members of the family Today we know that any properly equipped home should contain a clinical thermometer which any mother can retrieve at the proper time to detect illnesses early to the benefit of the family So it must be with the sphygmomanometer People can be entrusted with it Surely misuses and abuses will follow but in time with education and experience people will benefit from its use and the prevention and early treatment of hypertension will ensue and the morbidity and mortality from hypertension will certainly decline

A sturdy and reliable mercury type sphygmomanometer with a bell stethoscope can be purchased in New Orleans for about $50 00 tax included For the health and well being of the family therefore all homes should have a sphygmomanometer with someone trained to record the blood pressure (training is easy)

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Practolol in the treatment of tachyarrhythmias in patients with bronchial asthma

In patients suffering from bronchial asthma such cardiovascular diseases as hypertension and coronary disease are probably as common as in the general population Asthmatic patients frequently have arrhythmias during periods of severe airway obstruction Furthermore there are special problems in the

and 60 years and gives rise to the sudden appearance of congestive heart failure.[7] The pansystolic murmur is heard widely over the precordium, radiating to the second right intercostal space and into the supraclavicular area, suggesting concomitant aortic stenosis.[8-12] This results from the regurgitant jet being deflected forward and medially against the atrial septum only a few millimeters from the base of the aorta.[13,14] The diagnostic dilemma can be resolved only by careful auscultation which reveals the murmur to be holosystolic and not ejection in type. The ECG will show normal sinus rhythm. The teleroentgenogram of the heart will display a normal sized left atrium and left ventricle. By contrast, a flail anterior leaflet of the mitral valve occurs over a wide range of ages.[15] The symptoms of heart failure develop at various times, often remote to the initial detection of the murmur. The murmur itself is pansystolic at the apex and is associated with a thrill which may be felt over the posterior chest and mid portion of the thoracic vertebral column. The murmur may be heard on the top of the head and over the sacrum. These findings depend upon the regurgitant jet being deflected by the anterior leaflet so that it strikes the posterior wall of the left atrium.[11] If this structure abuts on the vertebral column, it is not surprising that the murmur and thrill are heard and felt in the areas mentioned. The ECG often discloses atrial fibrillation and left ventricular hypertrophy. The teleroentgenogram of the heart may reveal only minimal left atrial enlargement.[15]

The second but rarer complication is that of acute rupture of the ventricular septum. This lesion is usually associated with a holosystolic murmur accompanied by a systolic thrill. Both are appreciated maximally along the left sternal border. But again the presentation may be atypical, depending on the location of the perforation in the ventricular septum. Indeed, the murmur may be holosystolic at the apex without thrill and even radiate into the axilla, making it virtually indistinguishable from acute mitral insufficiency.[3,17] The presence of heart failure is common to both entities and is of no differential value. The location of the infarct as judged from the ECG is not helpful in making the diagnosis because both anterior and posterodiaphragmatic myocardial infarctions may be associated with either condition.[18] An early correct diagnosis of postinfarction ventricular septal defect is of considerable importance when one considers that this complication accounts for approximately 1 per cent of all deaths from acute myocardial infarction, that 24 per cent of those who die with this complication will do so within the first 24 hours,[19] and that surgical repair of the defect is not only possible but often life saving.[3]

The definitive diagnosis must rest on the demonstration of a left-to-right shunt at the ventricular level. Ideally the method used should be easy to perform, highly sensitive, and without danger to the patient. The hydrogen-sensitive platinum-tipped wire electrode amply fulfills each of these requirements.[4] This simple technique for left-to-right shunt detection can make the differential diagnosis between ruptured ventricular septum and mitral regurgitation secondary to papillary muscle dysfunction with ease at the bedside and may obviate the need of major cardiac catheterization.

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ever has a slight blocking effect on the bronchial β receptors it must be stressed that optimal bronchodilatation is obtained simultaneously preferably by one of the new broncho elective sympathomimetics

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Bedside diagnosis of postinfarction ventricular septal defect using the hydrogen-sensitive, platinum-tipped, wire electrode

Rupture of the muscular portion of the interventricular septum following an acute myocardial infarction was first described by Latham[1] in 1945 It is found in 0 66 per cent of autopsied persons who have died with acute myocardial infarctions[2] however only about a third of these are diagnosed before death[3]

We recently have observed a 67 year old man in whom a loud murmur was heard four weeks following a prolonged episode of severe chest pain His hospitalization was necessitated by progressive unremitting dyspnea

On physical examination the patient was in acute respiratory distress The blood pressure was 110/70 the pulse was 100 per minute and respirations were labored at 36 per minute The neck veins were distended at 90 and bilateral moist râles were present throughout both lungs A loud harsh Grade IV/VI holosystolic murmur was present. It was loudest at the left sternal border radiating under the sternum but not into the axilla Atrial (S_4) and ventricular (S_3) gallops were present An easily palpable systolic thrill was noted along the left sternal border The remainder of the examination was unremarkable

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The electrocardiogram (ECG) disclosed a resolving posterodiaphragmatic myocardial infarction while the chest teleroentgenogram revealed cardiomegaly and marked pulmonary congestion

To better define the murmur s etiology a simple study utilizing the technique of the platinum tipped hydrogen sensitive wire electrode[4,5] conclusively demonstrated the existence of a ventricular septal defect

The sudden appearance of a loud holosystolic murmur in the setting of an acute myocardial infarction suggests the development of one of two possible complications The first and most common is acute mitral insufficiency If both anterior and posterior leaflets are involved the customary apical holosystolic murmur will be heard radiating to the left axilla and often associated with a thrill The ECG in contrast to the chronic form of the disease shows normal sinus rhythm rather than atrial fibrillation Left ventricular and left atrial enlargement are also conspicuously absent on the teleroentgenogram[6]

Two special syndromes of mitral insufficiency have been described depending upon whether the posterior or the anterior leaflet is affected Disease affecting the posterior leaflet commonly is caused by rupture of the chordae tendinae which most frequently occurs in persons between the ages of 40

Table I Infectious complications of 97 placements of permanent transvenous pacemakers

	N
Wound infections	
Staphylococcus epidermidis (± Streptococcus pyogenes)	4
Staphylococcus aureus (± Strep pyogenes)	2
Escherichia coli	1
Proteus mirabilis	1
Bacterial endocarditis after wound infection	
Staphylococcus epidermidis	1
Staphylococcus aureus	1
P mirabilis	1

thoracotomy is medically contraindicated long term suppressive oral antibiotic therapy offers a possible alternative This depends upon the nature of the infecting organism We have recently attempted this with a *Proteus mirabilis* infection but were unsuccessful This may have been because of the higher antibiotic resistance of the organism than that of staphylococci (the minimal inhibiting concentration of ampicillin is 1 25 µg per milliliter that of cephalothin is 5 µg per milliliter) or because of the ability of enteric bacilli to develop resistance to penicillin drugs during treatment Numerous species of microorganisms have been isolated from patients with intraventricular foreign bodies including Candida[4] gram negative bacteria[5] and staphylococcus Fortunately the last appears to be the most common as it can be treated with one of the penicillins or cephalosporins and does not develop resistance to these even during prolonged therapy For the same reasons long term oral antibiotic suppression of such foreign body staphylococcal endocarditis is feasible Cephalexin since it is predictably well absorbed[6] and therefore gives more predictable blood levels than penicillins may be the preferable oral antibiotic in this circumstance

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Long-term suppression of foreign body endocarditis with cephalexin

Permanent transvenous endocardial pacing is employed frequently in patients with life threatening bradyarrhythmias especially those who are unable to tolerate thoracotomies[1] The ease is associated with a small but significant incidence of complications among which are wound infection bacterial endocarditis and septicemia[1,2] The last two complications almost invariably dictate removal of the transvenous catheter However fibrosis of the catheter tip to the right ventricular endocardium may be so firm that simple removal is not possible If this situation occurs with endocarditis in a patient unable to undergo thoracotomy it presents a considerable clinical dilemma We have recently cared for a patient in this circumstance and have succeeded in suppressing the infection for over two years using an oral cephalosporin antibiotic

The patient a 67 year old diabetic woman first had a transvenous pacemaker inserted in 1964 because of Adam Stokes attacks Battery failure in September 1967 required replacement A mixed infection of the skin pocket with group A *Streptococcus* and *Staphylococcus epidermidis* made another replacement necessary in November 1967 Attempts to remove the original intravascular catheter were unsuccessful because of firm fibrosis to the endocardium Therefore it was left in place In the ensuing year she was well except for occasional ill defined chills until December 1968 when she was first seen with fever This disappeared in 24 hours without treatment but in February 1969 she began to complain of episode of rigors not associated with obvious infection She entered the hospital in March 1969 For the next month she had repeated positive blood cultures for coagulase negative *Staphylococcus epidermidis* resistant to penicillin (20 units per milliliter) but sensitive to oxacillin (0 312 μg per milliliter) and cephalothin (0 312 μg per milliliter) She was given methacillin but developed an allergic rash so was given cephalothin 8 Gm per day intravenously for four weeks At the end of this treatment her blood culture again was positive She refused surgical removal of the catheter so was given 2 Gm of cephalexin by mouth per day She had rigors while receiving that dose so her maintenance dosage was increased to 3 Gm per day Since then she has had two episodes of chill and fever one with positive blood culture associated with failure to take the cephalexin She has had repeated urinalyses showing many white blood cells (WBC) but blood urea nitrogen (BUN) and liver function tests have been near normal Her hematocrit has risen during treatment from 35 to 42 Routine blood cultures and cultures done in L form media were sterile in May 1971 She is still taking cephalexin 3 Gm per day but experiences chills and night sweats if she omits several doses of cephalexin

Review of our hospital records reveal that 57 patients have had permanent transvenous pacemakers inserted since 1966 Twenty five have had one or more replacement procedures bringing the total insertions to 97 Thirty nine of the patients have been men 18 women Ages have ranged from 18 to 95 with the average age 68 years All patient received prophylactic antibiotics (oxacillin or cephalothin) immediately before and for two days after the operation Light wound infections occurred (Table I) with three episodes of bacterial endocarditis all in patients who had multiple replacement Six of the infections have been with organisms sensitive to the prophylactic drug Two of the three patients with endocarditis had their infections cured by removal of the pacemaker catheter and vigorous antibiotic therapy

Bacterial endocarditis is not a rare complication of permanent transvenous endocardial pacing Most of these patients can be cured with antibiotics and removal of the catheter even if fibrosis of the catheter to the endocardium has occurred[3] but occasionally this is not possible If as is often the case

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Wedensky inhibition

To the Editor

We wish to comment on the article Increase in threshold to ventricular activation related to atrial contraction a possible example of Wedensky inhibition " by Danzig and Diamond which appeared in a past issue of this JOURNAL (82 531 1971) The authors invoked Wedensky inhibition to explain the failure of an A V junctional impulse to be manifested and the failure of a pacemaker situated in the ventricle to excite the myocardium (Fig 3)

We would like to point out the results of experiments conducted recently in tissue bath preparations[1,2] and which may shed some light on the phenomenon described by Danzig and Diamond and perhaps on Wedensky inhibition in general It is possible to induce severe depression of excitability and responsiveness in a very short segment of cardiac tissue[1] When this is done block of variable degree including unidirectional block can be obtained even if cells distal to each end of the depressed segment are normal It was shown in a T-shaped preparation that the outgoing impulse which would have been expected from stimulation of one end of the preparation was extinguished and failed to exit if the second end of the preparation was stimulated with the appropriate time relationship

As a mechanism for this inhibition of excitation it was postulated that when the inhibitory end was stimulated the action potentials to which it gave rise invaded and died out in some part of the depressed tissue thereby diminishing its responsiveness. Those fibers would then be unable to take part in the excitatory wavefront expected from stimulation of the second end of the fiber

It was emphasized that while this mechanism resembles that of concealed conduction the important difference was that the impulse dies out in a depressed fiber rather than in a fiber made refractory by previous activity[2] This phenomenon of inhibition of excitation and impulse conduction may very well be the explanation for the phenomenon illustrated in Fig 2 of the article by Danzig and Diamond the inhibitory stimulus coming from the atrium (P wave) could travel through the depressed A V junction and His bundle with a long conduction time and die out in it making it less responsive to the inhibited impulse —i e the A V junctional rhythm originating in a different focus and travelling from a different direction The result would be inhibition of the A V junctional rhythm by the supraventricular impulse and failure of the A V junctional beat to exit and to propagate to the ventricle Since this phenomenon can be demonstrated in in situ Purkinje fiber preparations there is good reason to suspect that it may also occur in the heart in vitro especially in the A V junction since the latter structure is well known for its long impulse transmission time The presence of advanced A V block in the patient reported by Danzig and Diamond makes this even more likely

The electrophysiologic basis for the phenomena described by Wedensky especially Wedensky inhibition is not clear As Danzig and Diamond have themselves suggested critical timing is indeed of crucial importance in determining whether electrical impulses will be propagated or blocked We would like to suggest that inhibition of impulses related to critical time relationships as demonstrated in depressed preparations of cardiac tissue could well be the underlying mechanism for Wedensky inhibition. This mechanism cannot explain failure or delay of ventricular depolarization by the ventricular pacemaker but the authors themselves provide an adequate explanation—catheter motion cannot be excluded and indeed it is probably wise to diagnose pacemaker ventricular block only if it can be reasonably certain that the electrode tips are in constant contact with the myocardium.

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Reply

To the Editor

I have reviewed the Letter to the Editor from Drs Klein Cranefeld and Hoffman concerning the paper which appeared in the AMERICAN HEART JOURNAL (82 531 1971)

Letters to the Editor

Regional blood sampling for assessing metabolic changes in myocardium

To the Editor

We were interested to see the article by Obeid and co workers in a recent issue (Am Heart J 83 189 1972) stressing the importance of regional blood sampling in assessing the blood metabolic changes following coronary artery ligation We were gratified to find that these authors found results which were essentially similar to ours[1,2] as far as changes in glucose lactate and potassium are concerned However, we were rather surprised to note only a passing reference to our previous long publication stressing the advantage of regional blood sampling[2] A major point of our previous publications has been that local venous sampling is desirable in assessing regional metabolic change as now also argued by the present authors

The increased glucose arteriovenous difference across the ischemic myocardium with lactate production was previously reported by us[1,2] Release of potassium into local venous blood without significant arrhythmias is also a finding we have described[3]

It should also be noted that a technique for regional sampling in a closed chest preparation has been devised by Regan and associates[4] by inserting the coronary sinus catheter extremely deep into the anterior cardiac vein

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Reply

To the Editor

The letter by Opie Owen and Thomas raises some points that need clarification In the first place we have acknowledged and appropriately referred to the work of Opie and his group[1] on the importance of regional sampling in studying metabolic changes during acute myocardial ischemia Since our paper was not an exhaustive review of the subject we had to be selective in the choice of bibliography

Secondly the technique of sampling that we described utilized retrograde catheterization of the great cardiac vein through the coronary sinus with positioning of the catheter tip deep in the vein that runs along the anterior descending coronary artery at approximately the level of the arterial ligature Thus we avoided dissection of the vein rinsing and other interventions inherent in the Seldinger technique that Opie and co-workers[2] utilized for regional sampling We were also able to perform more selective sampling of local venous drainage of the ischemic myocardium than was described by Regan and coworkers[4] who positioned the catheter tip at the junction of the great cardiac vein with the coronary sinus In two experiments (not included in our report) the catheter could not be introduced any further than the junction of the great cardiac vein with the coronary sinus and metabolic data on samples obtained from that site following ligation of the anterior descending coronary artery were not significantly different from those obtained from the main body of the coronary sinus

Thirdly we not only confirmed the observations on local metabolic changes related to glucose lactate and potassium following coronary ligation but we extended the observation to include pH and P_{O_2} the latter showing interesting findings that we discussed in our paper

Finally our results offer quantitative metabolic data that were statistically analyzed and that could be used as baseline for further studies of regional metabolic changes in the effluent drainage of the ischemic myocardium

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To the Editor

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We would like to point out the results of experiments conducted recently in tissue bath preparations[1,2] and which may shed some light on the phenomenon described by Danzig and Diamond and perhaps on Wedensky inhibition in general It is possible to induce severe depression of excitability and responsiveness in a very short segment of cardiac tissue[1] When this is done block of variable degree including unidirectional block can be obtained even if cells distal to each end of the depressed segment are normal It was shown in a T-shaped preparation that the outgoing impulse which would have been expected from stimulation of one end of the preparation was extinguished and failed to exit if the second end of the preparation was stimulated with the appropriate time relationship

As a mechanism for this inhibition of excitation it was postulated that when the inhibitory end was stimulated the action potentials to which it gave rise invaded and died out in some part of the depressed tissue thereby diminishing its responsiveness Those fibers would then be unable to take part in the excitatory wavefront expected from stimulation of the second end of the fiber

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Reply

To the Editor

I have reviewed the Letter to the Editor from Drs Klein Cranefield and Hoffman concerning the paper which appeared in the AMERICAN HEART JOURNAL (82 531 1971)

I would like to thank them for their comments which provide a possible electrophysiologic explanation for the electrocardiographic observations described in the paper. I do not think we should consider catheter motion the only possible explanation for the failure or delay of ventricular depolarization by the ventricular pacemaker, but their points are well taken.

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Terminology in catheter marking

To the Editor:

I have recently noticed an inconsistency in the use of certain medical terminology. Because this inconsistency could cause misunderstandings which might even endanger the life of a patient, I would like to bring it to the attention of your readers.

The terms "proximal" and "distal," meaning "near" and "far," are always used anatomically with respect to the midline or trunk of a patient or experimental animal and are so defined in Stedman's Medical Dictionary, 20th Edition. In the descriptive literature and the instructions for various catheters and pacing electrodes, however, the manufacturers refer to the ends of the catheter also as "proximal" and "distal," but with respect to the physician handling the catheter. Thus, the end of the catheter that is "proximal" with respect to the patient is "distal" with respect to the physician and vice versa. In many catheters this conflict is not likely to cause confusion because the ends of the catheter are sufficiently different in design to leave no doubt as to which end is which. In certain types of bipolar pacing electrodes, however, the two ends of the catheter look very similar and it is not a obvious as to which end to introduce into the patient and which end to connect to the pacemaker. Similarly, the connectors in many multi-lead and multi-lumen catheters are simply marked "proximal" and "distal," which can leave doubts as to how to connect the catheter.

This rather confusing ambiguity could easily be avoided by referring to the ends of the catheter as "tip end" and "connector end" instead.

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Book reviews

PRACTICAL ELECTROCARDIOGRAPHY ed 5 Henry J L Marriott M D Baltimore 1972 The Williams & Wilkins Company 325 pp Price $10 50

Marriott s book of Practical Electrocardiography has enjoyed a great success in training many physician in electrocardiographic interpretation and this new edition continue a fine tradition. The volume written for doctors continues to place its emphasis on cardiac arrhythmias a field of particular intere t to Marriott The author has kept the book simple lucid and clearly illustrated with well selected tracings Up to date and in tended for beginners the book is directed to practical clinical cardiolo y as i clearly indi cated by the author s purposeful refusal to develop the concept of Hi bundle electrograms or the interpretation of rare and more complex a pect of electrocardio raphy This fifth edition i highly recommended to all who wi h to learn electrocard ography

HEART BLOCK Richard S Co by M D and Michael Bilitch M D New York 1972 McGraw Hill Book Company Inc 251 pp Price $12 95

Cosby and Bilitch have described their experience with heart block at the Los Angeles County Hospital Included are the anatomy and electrophysiology of the normal heart classification of block pathology hemodynamic changes clinical course electrocardiographic manifestat ons and treatment The major emphasis in treatment is on the use of pacemakers This is proper for com plete heart block but the prevention of block and advanced heart disease mu t not be for gotten. The illu trations are well chosen although the hi tologic illustrations are not of high quality and not convincing This is to be expected because of the great similarity of cardiac muscle and conduction tissue when viewed with the light microscope Nevertheless the authors have ac cumulated much useful material into a sin le volume that presents concepts related to heart block an important cardiologic problem. Those who wish also to learn the opinions and practices of the authors will find them well described in this small monograph The book is intended and recommended for the practicing doctor as well as for those training in internal medicine and cardiology

Books received

ANNUAL REVIEW OF MEDICINE Volume 23 1972 Edited by Arthur C DeGraff A sociate Editor William P Creger Palo Alto 1972 Annual Reviews Inc. 515 pages Price $10 00

ANAESTHESIA IN ORGAN TRANSPLANTATION Edited by T Hilary Howell and Alan W Grogono New York 1972 Intercontinental Medical Book Cor porat on, 1i0 pages Price $22 50

ATLAS OF NUCLEAR MEDICINE Volume 3 Reticulo-endothelial System Liver Spleen and Thyro d By Frank H DeLand M D and Henry N Wagner Jr M D Philadelphia 1972 W B Saunders Com pany 293 page Pr ce $21 00

HAMDARD Volume XIV (Special ue) July through September 1971 Edited by Hakim Mohammed Said Pakistan 1971 The Institute of Health and Tibbi (Medical) Research under the auspices of the Hamdard National Foundation 505 pages Price $26 50

LECTURES IN CARDIOLOGY—A LISTENER S NOTEBOOK Edited by Sylvan E Moolten M D Philadelphia 1972 The Charles Press Publishers Inc 281 pages Price $7 50

RÉANIMATION ET MEDECINE D URGENCE—1971 Edited by M Goulon and M Rapin Paris 1971 L Expan sion Scientif que Francai e 333 pages

RESPIRATION IN HEALTH AND DISEASE Ed 2 By Reuben M Cherniack M D Louis Cherniack M D and Arnold Naimark M D Philadelphia 1972 W B Saunders Company 496 pages

Announcements

Tenth annual cardiology seminar

The Tenth Annual Cardiology Seminar sponsored by The Rogers Heart Foundation will be held at the Holiday Inn Freeport Bahama Island on December 1–4 1972 For further information please write Henry J L Marriott M D The Rogers Heart Foundation St Anthony s Hospital St Petersburg Fla 33705

Cardiology symposium

The University of Texas Graduate School of Biomedical Sciences at Houston Division of Continuing Education will sponsor a Cardiology Symposium to be held in Houston Texas on December 4–7 1972

The program will present an intensive review of cardiology The guest lecturer will be Dr S Gilbert Blount Jr Professor of Medicine and Head Division of Cardiology University of Colorado Medical School Denver Colorado

For further information please contact Office of the Dean University of Texas Graduate School of Biomedical Sciences at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

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Editorial

The role of infarctectomy in the surgical treatment of myocardial infarction

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Since the exciting report of Heimbecker Lemire and Chen[1] in 1968 on experimental results and the clinical application of infarctectomy great interest has developed in the potential role of excision of infarcted myocardium as a means of salvaging the patient with hemodynamic deterioration following myocardial infarction Infarctectomy—i e the excision of demarcated infarcted muscle within two weeks after the clinical occurrence of myocardial infarction—is to be differentiated from the resection of a ventricular aneurysm or dyskinetic myocardium several weeks to months after the infarction Although several isolated reports of success following excision of necrotic myocardium have appeared[2-4] this mode of therapy has not received wide application Recent experience suggests that the indications for myocardial infarctectomy are not susceptible to a simplistic analysis The procedure may or may not be beneficial under certain circumstances and forms only a part of the larger and more complex problem of left ventricular power failure secondary to myocardial infarction

Particularly pertinent is the observation that infarctectomy has met with the greatest success in those instances in which the infarct was complicated mechanically by the presence of a ventricular septal perforation[1,4] The surgical treatment of this uncommon complication of myocardial infarction has itself undergone a very interesting evolution Patients whose recovery from myocardial infarction has been complicated by the development of a ventricular septal defect (VSD) have frequently been tided over the early critical period after infarction by appropriate intensive medical management Interval repair of the VSD weeks to months after the infarct generally has been successful[6] Certain patients however following the development of a VSD deteriorate rapidly with failure and even shock consequent to the additional burden on the injured myocardium of a large left to right shunt Attempts at surgical correction of the defect in the first two weeks after myocardial infarction have often failed[7] Early attempts were usually undertaken through a right ventriculotomy the surgical approach ordinarily employed

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for correction of congenital VSD's. This approach, despite its historical precedent, traumatizes the already overburdened right ventricle, may interrupt collaterals from the right coronary artery, and last but not least, fails to completely correct the conditions leading to the patient's deterioration. More recently, closure of the septal defect through an incision in the left ventricular infarct with complementary excision of the infarct has yielded excellent results.[1-6] In such instances it may be difficult to assess the relative importance of closure of the defect as opposed to infarct excision. Undoubtedly, both lesions may contribute substantially to the patient's hemodynamic deterioration and correction of both defects may be required for a successful result.

On the other hand, excision of infarcted muscle in the absence of an associated mechanical complication such as a VSD or a ruptured papillary muscle has not met with the same degree of success. This is not surprising when one considers the pathology of cardiogenic shock following myocardial infarction. Page and associates[8] have described the cardiac pathology in 20 patients dying in cardiogenic shock. Quantification of muscle loss indicates that the occurrence of cardiogenic shock is associated with loss of 40 to 70 per cent of the left ventricular myocardium. Loss of myocardium appears to be additive in relation to old and new infarcts. Thus simple excision of infarcted myocardium cannot necessarily be expected to improve cardiac performance or output, as confirmed by Lewis and Hammond[9] in their experimental studies, particularly when removal of large amounts of myocardium may result in a critical reduction of left ventricular volume.[10-12]

In the course of a fairly large experience with the treatment of surgical complications of myocardial infarction, we have undertaken infarctectomy as the sole treatment mode in only two instances.[6] In one patient who presented with cardiogenic shock early in our experience, resection of the infarct to the base of the papillary muscles resulted in a completely inadequate cardiac output due to a critical reduction of left ventricular volume. In the second patient, a young man 34 years of age who had experienced his first myocardial infarction, shock was associated with uncontrollable ventricular arrhythmias. Institution of intra-aortic balloon mechanical assistance stabilized the patient's hemodynamics, but recurrent ventricular fibrillation continued despite all available medical measures. Subsequent excision of an apical infarct, the source of the ventricular arrhythmias, yielded a successful result. Mundth[13] has reported the Massachusetts General Hospital experience with 25 patients in whom resistant cardiogenic shock was treated by a combined approach of intra-aortic balloon pumping and subsequent emergency myocardial revascularization with aortocoronary saphenous vein bypass grafts. Of these 25 patients, 16 underwent infarct or aneurysm resection in combination with revascularization. In each instance the decision to carry out infarctectomy was based on the following considerations: (1) the presence of a large paradoxically contracting infarct or aneurysm which appeared to interfere with left ventricular mechanics; (2) a localized area of infarct associated with recurrent ventricular arrhythmias; (3) thinned out necrotic myocardium wherein rupture appeared imminent; and (4) a noncontracting area of myocardium which appeared to be contributing to impaired cardiac output in a patient who could not be separated from cardiopulmonary bypass after revascularization. In no instance was infarctectomy selected as the primary or sole method of choice for treatment of this type of patient.

Viewed from this standpoint, it seems apparent to us that infarctectomy will find appropriate application in certain patients in whom a localized area of infarction causes either an electrical or hemodynamic defect out of proportion to the area of muscle loss. Similarly, infarctectomy is indicated in those situations in which the myocardium must be incised to repair an intracardiac defect such as a VSD. In such instances excision of the infarct does the least injury to the myocardium and in selected instances it may actually improve hemodynamics.

Much attention has been directed recently to defining the size of the infarct by electrical mapping or by means of indicator dyes. The development of such techniques implies a fundamental benefit to be derived from infarct excision, a position which may

not be wholly supportable The simple maneuver of applying suction to a cannula within the left ventricular chamber causes necrotic myocardium or scar to invaginate with rather clearly defined borders This phenomenon is based on the fact that non viable areas in the left ventricular wall do not withstand this type of physical force as does the adjacent normal muscle [14] This type of physical change in necrotic or scarred myocardium appears related to loss of wall thickness and mass in the area involved a factor which may not be apparent by examining the exterior of the ventricle when the left ventricular cavity is filled with blood

Finally any therapeutic method directed at the heart requires simultaneous consideration of anatomy and function on a moment-to-moment basis Removal of infarcted myocardium cannot be considered in the same context with tumor excision as applied to other organs The successful treatment of patients in cardiogenic shock following myocardial infarction requires a complete understanding and acceptance of the pathology which leads to cardiogenic shock as described by Page and colleagues [8] Thus in the vast majority of patients who present with this condition the functional loss of left ventricular myocardium at the time that shock develops is sufficient to be incompatible with life despite the most sophisticated pharmacologic management Attempts at salvage of such patients by surgical means is based on the premise that a substantial part of the nonfunctioning left ventricular myocardium is ischemic but viable Implicit in this statement is that survival depends on the restoration of function to the ischemic areas of muscle Infarctectomy by itself clearly does not meet these requirements The combined approach of mechanical cardiac assistance through balloon pumping in patients with cardiogenic shock as described by Buckley and co workers [9] followed by selective coronary arteriography left ventricular cineangiography and subsequent emergency revascularization[12,15] is a rational approach which has yielded promising results in a small series of patients In certain of these patients infarctectomy will undoubtedly be beneficial and even be required for a successful result based on the criteria set forth herein At the present time we believe that infarctectomy is indicated for those patients in whom a localized infarct contributes disproportionately to ventricular dysfunction or serves as a source for resistant arrhythmias A primary indication for infarctectomy is that situation in which incision through the infarct provides the safest and least deleterious avenue to repair an intracardiac abnormality such as a septal perforation Patients in whom emergency revascularization has been done for cardiogenic shock often need a complementary infarctectomy for a successful result

The concepts set forth here regarding infarctectomy must be considered tentative in this rapidly changing field Continuing studies on ventricular geometry and the limitations of ventricular volume will be required before any definitive statement is warranted on the role of infarctectomy in the treatment of myocardial infarction Despite the great success achieved by pharmacologic and electrical therapy of ventricular arrhythmias there will remain the occasional patient in whom excision of the irritable focus is essential Efforts to define such patients and to locate the irritable focus by epicardial mapping will be important to the salvage of patients in whom cardiac pumping performance is intrinsically adequate In other instances studies will be required to define the limits of ventricular volume It may be possible to resect a relatively large area of paradoxically contracting infarct if ventricular volume is restored by insertion of a prosthetic patch as suggested by Collins and Collins [16] Only with the clarification of these problems by further investigation can the ultimate role of infarctectomy be accurately stated

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Clinical communications

Clinical electrocardiographic and vectorcardiographic diagnosis of left posterior subdivision block, isolated or associated with RBBB

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Recent investigations carried out in dogs demonstrated the alterations of the ventricular activation process as well as the peripheral electrocardiographic (ECG) and vectorcardiographic (VCG) changes produced by the block of the posterior subdivision of the left bundle branch of His (LPSB).[1-3] These experimental findings permit the recognition of LPSB in clinical ECG and VCG tracings in a more accurate way than that proposed by other authors.

Modifications produced by LPSB on the electrical signs of a posteroinferior myocardial infarction and on the electrical manifestation of right bundle branch block are analyzed. Emphasis is placed on the differential diagnosis between LPSB and the *intra-* and peri-infarction blocks.

The diagnosis of LPSB was based on experimental findings[1-3] which demonstrated that this block delays the activation process in the posterior portion of the interventricular septum in all of the cases, whereas in the central portion it is delayed only in one third of the cases. The entire thickness of the posterior aspect of the free left ventricular wall was the region most affected by the block and displayed a progressive delay from apex to base. The most outstanding experimental ECG data were: (1) increased voltage of R waves in Leads II, III, and aVF, with a slurring of 22 msec. in the downstroke of this wave; frequently a notch in the same location was also present; (2) delayed onset of the *intrinsicoid deflection* in Leads II, aVF, and often in Lead V_6; (3) in some cases a Q wave appeared or it was augmented if previously present in Leads III and aVF; (4) generally the ÂQRS remained essentially unmodified; (5) QRS duration increased by about 18 msec. (average); (6) in most of the cases the T wave became negative in Leads II, III, and aVF; and (7) atrioventricular conduction was not altered.

The most outstanding experimental VCG data were: (1) the area situated below the X axis was markedly augmented, whereas the terminal area situated above this axis diminished or disappeared; (2) the initial and intermediate portions of the curve were consistently slurred; (3) the terminal segment was slurred in most cases; and (4) the curve showed a clockwise rotation in the frontal plane and a counterclockwise rotation in the horizontal plane.

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Table I Data for 17 patients

Case No	Age	Sex	Diagnosis
1	33	M	Apparently healthy heart
2	70	M	ASCVD * septal and diaphragmatic infarction
3	65	M	ASCVD septal infarction
4	44	M	ASCVD diaphragmatic infarction
5	68	M	ASCVD, septal infarction
6	64	M	Probable ASCVD (asymptomatic)
7	38	M	Coxsackie virus myocarditis
8	62	M	ASCVD septal infarction
9	68	M	ASCVD dorsolateral infarction
10	42	M	ASCVD septal and diaphragmatic infarction
11	69	M	ASCVD anteroseptal and diaphragmatic infarction
12	70	M	ASCVD diaphragmatic infarction
13	60	M	ASCVD diaphragmatic infarction
14	65	F	Probable ASCVD probable diaphragmatic infarction
15	51	M	ASCVD aortic stenosis probable diaphragmatic infarction
16	68	M	ASCVD diaphragmatic infarction
17	43	M	ASCVD diaphragmatic infarction

*ASCVD = atherosclerotic cardiovascular disease

Material and methods

In this paper an analysis of 17 clinical ECG and VCG records is presented The age of the patients ranged from 33 to 70 years Table I includes the most important data of each patient Sixteen were men and one was a woman Thirteen had proved and two had probable atherosclerotic cardiovascular disease one patient had viral myocarditis and one did not report clinical signs of cardiovascular disease

In twelve cases myocardial infarction was present, six were localized in the diaphragmatic aspect of the free left ventricular wall two were septal two others were combined septal and posteroinferior infarcts one was concomitantly diaphragmatic, septal and anterolateral and another was dorsolateral Two other patients had probable posteroinferior infarction Additional details of some patients are indicated in the legends to the figures

Vectorcardiograms were obtained using the Grishman cube system [8] In 6 patients the Frank system was also employed [9] The tracings were recorded by means of the vectorcardiograph model PV 3 (Hart Electronics Company) Intensity modulation interrupted the oscilloscopic beam each 1/500 or 1/1,000 of a second Several photographs of frontal, horizontal and left sagittal planes were made with a model C 4 C kymograph camera (Grass Instrument Company) Corresponding ECG were recorded either with a Sanborn Cardiette photographic apparatus or with a direct inscription device

Results

A *Electrocardiographic findings* QRS complexes had a duration ranging between 55 and 145 msec (average 112 msec) In isolated LPSB ÂQRS was in the fourth quadrant (averaging +50 degrees) in most of the cases in one case only ÂQRS was at +95 degrees In two cases of LPSB associated with RBBB the ÂQRS was at +85 degrees in one case and at +150 degrees in another

The intrinsicoid deflection in aV_F ranged from 50 to 80 msec (average 70 msec) The ventricular complexes were of qR or QR type in aV_F in all cases

Many cases showed an initial slurring of the R wave in aV_F (sometimes also in Leads II and III) with a duration of the slurring ranging from 10 to 30 msec (average 16 msec) In three cases a prominent notch was also observed in the same location All the cases showed in the downstroke of the R wave in Leads III and aV_F a slurring lasting from 15 to 60 msec (average 37 msec) frequently a notch was also present with the same location In some cases slur

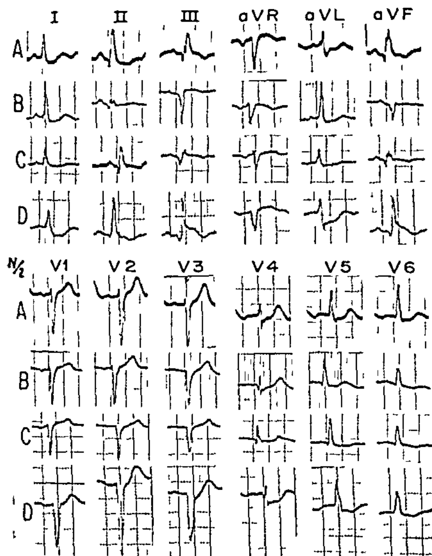


Fig. 1. Tracing of patient with atherosclerotic cardiovascular disease. (See text.)

rings and notches were also observed in the downstroke of the R wave in V_5 and V_6, particularly in vertical hearts.

The tracing presented in Fig. 1 belongs to a patient with atherosclerotic cardiovascular disease. Tracing *A* corresponds to the control tracing which shows ÂQRS at + 55 degrees and a QRS duration in Lead II of 130 msec. The R wave in aV_F has a high voltage, the intrinsicoid deflection at 60 msec, a plateau lasting 40 msec, and irregularities and a slurring of 60 msec in its downstroke. The intrinsicoid deflection in aV_L is at 40 msec. Deep S waves in right precordial leads and a notch in the downstroke of the R in V_5 are observed. These features suggest LPSB while the Q wave of Leads II, III, and aV_F suggests diaphragmatic myocardial infarction. Deep S waves from Leads V_1 through V_3 could suggest left ventricular enlargement. Tracing *B* was recorded a few hours later: the signs of LPSB disappear and the voltage of the S waves in right precordial leads decreases and there is a decrease in the R wave in V_6 as well. There

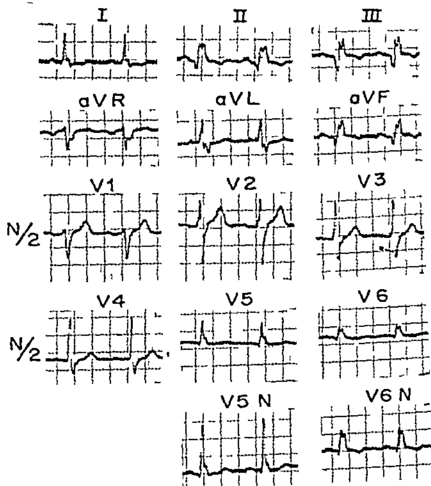


Fig. 2. ECG tracing. The AQRS is at +50 degrees. The ventricular complexes in Lead III and aVF show a deep and slurred Q wave and an R wave with a plateau of 60 msec. The intrinsicoid deflection in aVF is at 170 msec. In Leads I and V_6 there are qR complexes with a terminal notch of the R. Lead V_4 shows qR complexes with a plateau of the R wave of 4? msec. The width and shape of the ventricular complexes in the posteroinferior (Leads II, III, and aV_F) and the lateral aspect (V_6) demonstrate an important delay of the activation of those regions due to a LPSB associated to a posteroinferior myocardial infarction. The diagnosis of classical left bundle branch block is easily discarded by both the ECG and VCG.

are QS complexes in Leads III and aV_F and a slurred Q wave in Lead II suggesting clearly a diaphragmatic infarction and the ventricular complexes in Leads V_1 through V_4 indicate an infarction of the inferior half of the interventricular septum. Tracing C was recorded two days later and shows again a slurred terminal R and a Q wave of 35 msec in aV_F. These changes indicate the reappearance of the LPSB of lesser degree than in tracing A. Tracing D was recorded 30 days later, coinciding with an attack of coronary insufficiency. The voltage of the R wave in Leads II, III, and aV_F as well as the voltage of the S wave in right precordial leads increase again remarkably indicating a greater degree of LPSB. It is worthwhile to call attention to the reduction of the pathologic Q wave in tracings C and D due to LPSB (see the discussion).

In Figs. 2, 4, and 5 other ECG examples of LPSB without RBBB are presented.

B. *Vectorcardiographic findings.* The QRS loop had a duration close to that of the QRS complex in Lead II. The VCG frontal plane (*F*) had a clockwise rotation and most of the curve was situated below the origin of the curve (E point). Sometimes a small counterclockwise curl was observed in the intermediate portion of the curve. The VCG horizontal plane (*H*) had a counterclockwise rotation, but in one case it was clockwise due to a septal infarction extending to the left ventricular wall. All the VCGs

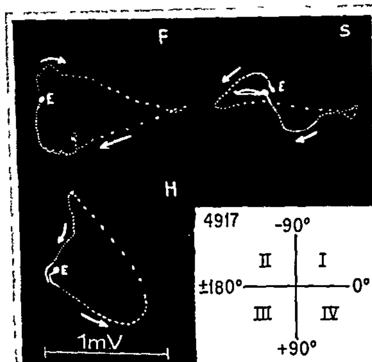


Fig. 3. Example of LPSB complicating a postero-inferior myocardial infarction. The VCG was taken by the Frank system and corresponds to the ECG of Fig. 2. One dash = 1.1 millisecond. (See text.)

showed slurrings at the initial portion in the three planes and these ranged from 13 to 30 msec (average 22 msec). These slurrings were generally situated in quadrant III and sometimes in quadrant IV. In the horizontal plane this slurred portion had a variable situation (for delimitation of quadrants in the frontal and horizontal planes see Fig. 3).

All the VCGs showed slurrings at the terminal portion with a duration ranging from 14 to 56 msec (average 27 msec) situated in quadrants III and IV of the frontal plane (see Fig. 3). Only in two cases a small terminal portion reached quadrant II. In the horizontal plane this slurred portion was situated in quadrants I and II and when right bundle branch block coexisted it was mostly in quadrant III (see Fig. 6). The interval from the E point to the most inferior dash of the VCG frontal plane (*F*) showed a close correlation with the intrinsicoid deflection in aV_F.

Fig. 3 shows the typical VCG findings of LPSB (tracing recorded using the Frank system). The curve has an initial slurring lasting 19 msec and another terminal slurring lasting 56 msec. The VCG frontal plane (*F*) has a clockwise rotation while the VCG horizontal plane (*H*) rotates in a counterclockwise direction. In the frontal plane the interval from the E point to the X axis is 27 msec and most of the curve is below this axis. This tracing suggests posteroinferior myocardial infarction, LPSB, and true posterior or dorsal involvement of the free left ventricular wall.

In Figs. 4 and 5 other VCG examples of LPSB without RBBB are presented.

LPSB associated with right bundle branch block (RBBB). Fig. 6 is an example of LPSB associated with RBBB (Case No. 7).

ECG. The curve shows an $S_I Q_{III}$ pattern. ÂQRS is at +85 degrees. The ventricular complexes in Leads II, III, and aV_F are of qR type and qRs in Leads V_4, V_5, and V_6. Ventricular complexes in V_1 are of rsR type while in aV_R they are rS type. The intrinsicoid deflection is at 65 msec in aV_F, V_5, and V_6 and at 40 msec in aV_L. R waves

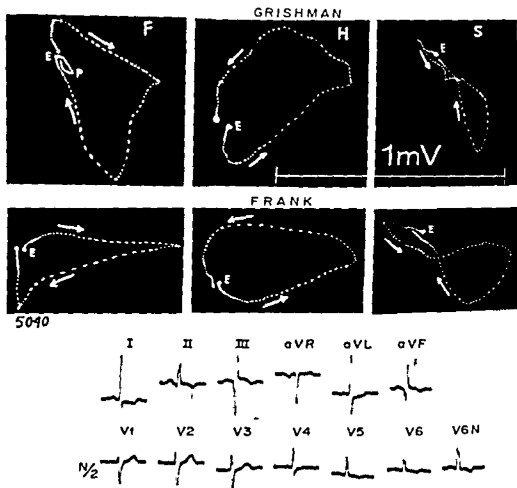


Fig 4 ECG and VCG curves of a posteroinferior myocardial infarction associated with LPSB One dash = 1.1 millisecond In the ECG tracing the AQRS is at +20 degrees and there is an S_1Q_3 pattern Leads III and aV_F show deep and slurred Q waves The ventricular complexes in aV_F are of QR type with slurring of the terminal portion of the downstroke of the R and intrinsicoid deflection at 65 msec Lead V_6 shows qR complexes with a plateau of 25 msec and intrinsicoid deflection at 60 msec This ECG demonstrates a remarkable delay of the activation in the posteroinferior and lateral aspects of the left ventricular wall In the VCG the tracings of the upper panel were obtained using the Grishman cube system The curve shows an initial slurring of 16 msec and another terminal slurring of 23 msec The VCG frontal plane (*F*) has a clockwise rotation and the VCG horizontal plane (*H*) has a counterclockwise rotation The interval from the origin of the curve to the X axis in the frontal plane is 32 msec The curves recorded with the Frank system show slight difference in morphology but they present essentially the same features mentioned above The Q loop is well defined in the Grishman but not in the Frank system Both the ECG and VCG suggest posteroinferior myocardial infarction and LPSB

in Leads III and aV_F show a notch in the downstroke and the initial portion of the upstroke is slightly slurred

In this case the leads exploring the posteroinferior aspect (III and aV_F) and the lateral aspect (V_5 and V_6) of the free left ventricular wall demonstrate a remarkable activation delay in those regions

VCG Most of the curve is below the E point The VCG frontal plane (*F*) and the VCG horizontal plane (*H*) have a clockwise rotation except for the initial portions (Q loop) that have a counterclockwise rotation There is an initial slurring lasting 30 msec and another terminal slurring of 34 msec In the horizontal plane the QRS loop is situated forward and mainly to the left from the E point and there is a small terminal portion at the right

The ECG of this figure shows rS complexes in aV_R instead of the QR complexes expected by the presence of a RBBB The

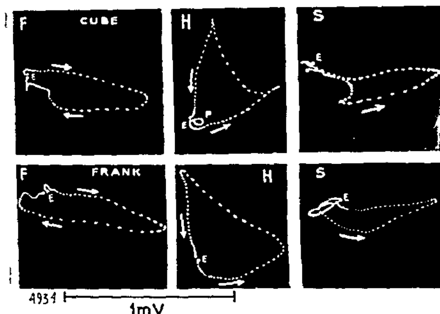


Fig 5 One dash = 1 1 millisecond In the upper panel is the VCG obtained using the Grishman cube system which shows an initial slurring of 15 msec and another terminal slurring of 35 msec The VCG frontal plane (*F*) has a clockwise rotation and the VCG horizontal plane (*H*) has a counterclockwise rotation In the lower panel is the VCG obtained using the Frank system showing a larger S loop compared with the cube system nevertheless it presents essentially the same features Both systems loops may suggest posteroinferior necrosis These tracings suggest LPSB in a semihorizontal heart They correspond to a patient who has always been asymptomatic

VCG shows only a small portion of the S loop above the X axis in the frontal plane (see the discussion)

These tracings correspond to a patient suffering a Coxsackie virus myocarditis and no heart enlargement was observed in the chest films

Discussion

LPSB delays the electromotive forces in the posterior portions of the interventricular septum and in the posterior aspect of the free left ventricular wall This fact can be represented by a vector directed backward downward and more or less to the left depending on the electrical position of the heart [1,2]

The activation of the posterior aspect of the free left ventricular wall can be mainly recognized by the delay of the intrinsicoid deflection in aV_F and sometimes also in V_5 and V_6 In cases of LPSB complicating a posteroinferior myocardial infarction the latter also contributes to delay the intrinsicoid deflection in the mentioned leads Nevertheless in cases without infarction this delay should be solely attributed to the block [4]

The ECG as well as the VCG demonstrated early alteration of the ventricular activation Thus in many cases the ECG had a slurring and/or a notch in the initial portion of the upstroke of the R in aV_F (and sometimes also in Leads II and III) whereas in all cases the VCG showed a slurring of the initial portion in the three planes This is due to the fact that there is a variable but significant contribution of the posterior subdivision to the activation of the interventricular septum

LPSB invariably delays the posterior terminal electromotive forces of the ventricular activation with marked manifestations in both the ECG (slurring of the downstroke of the R in Leads III and aV_F) and the VCG (slurring of the terminal portion of the curve) This delay is more prominent in the human heart than in the dog [3]

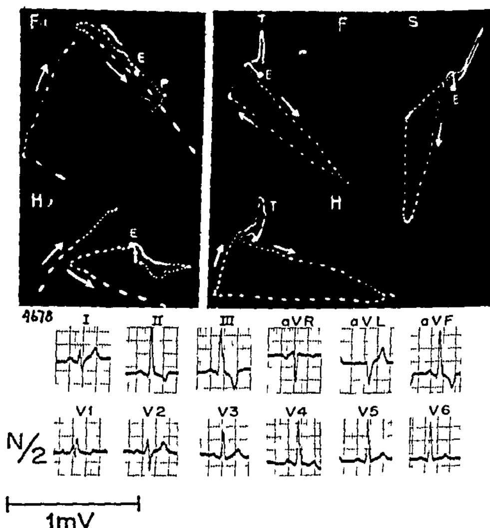


Fig 6 ECG and VCG of a patient with RBBB plus LPSB (case No 7) One dash = 2 0 millisecond Increased voltage of Q loop in frontal plane (See text)

This is due to the fact that in man the activation of the basal portion of the heart takes longer because the Purkinje fibers are almost absent in those areas and the ventricular wall is thicker Consequently the delay caused by LPSB must be more pronounced and the electrical manifestation of slowed conduction is more prominent in both the ECG and the VCG

It is necessary to emphasize that the ECG manifestations of LPSB vary according to the electrical position of the heart[1, 6, 7] Thus in vertical hearts Leads II, III and aV_F (exploring the posterior left ventricular aspect) reflect more accurately the manifestations of the block In horizontal hearts, the features manifested in those leads are variable especially in aV_F These variations were also observed experimentally by changing the heart from the vertical to the horizontal position In both vertical and horizontal hearts Leads V_5 and V_6 may reflect potential variations of areas affected by the block showing a delayed intrinsicoid deflection and slurrings or notches of the R wave These findings were observed in some of the cases studied in this paper (Figs 2, 4 and 6)

LPSB and necrosis of the posterior aspect of the free left ventricular wall Recent experimental work carried out in our laboratory demonstrated that LPSB modifies the electrical manifestations of a necrotic area of 2 5 by 3 cm produced in the posterior aspect of the free left ventricular wall[4] The following facts were observed

When the experimental necrosis was transmural or subepicardial showing QS complexes in Leads III and aV_F the association of LPSB originated qR or QR complexes in those leads

In subendocardial necrosis the ventricular complexes in Leads III and aV_F were of Qrs type and the activation of the preserved area overlying the necrotic tissue was moderately delayed as demonstrated by direct epicardial bipolar leads When LPSB was added the ventricular complexes in Leads III and aV_F became of qR or QR type—i e the previous S wave disappeared and the R wave increased while the Q wave diminished

In the presence of intramural necrosis the ventricular complexes in Leads III and aV_F were of Rs type The association of LPSB gave rise to R type complexes i e the S wave disappeared and the R augmented in voltage

These experimental findings demonstrated that when a posteroinferior myocardial necrosis is complicated with LPSB the electrical manifestations of the necrosis are reduced or even masked These facts were also observed in clinical tracings as in Panels *C* and *D* of Fig 1 This is due to the fact that the delayed activation of the preserved areas of the posterior aspect of the left ventricular wall originate electromotive forces with sufficient magnitude to be recorded in peripheral leads Thus the electrical signs of necrosis in Leads III and aV_F are changed and the extent of the necrosis in these cases is difficult to evaluate

LPSB intrainfarction and peri infarction blocks The delayed activation of surviving strands of muscular tissue included in an infarcted area has been named intrainfarction block and the initial slurring of the VCG of a patient with myocardial infarction has been thought to be due to intra infarction block [13] The resultant vectors from the activation of the surviving cells should point toward the site of the infarction but reaching insufficient magnitude to counterbalance vectors pointing away from the infarction It can be thought that the activation of those cells gives rise to notching of the Q wave of necrosis and to the initial slurrings of the VCG loop [4] In the case of posteroinferior myocardial infarction associated with LPSB these notchings and slurrings of the intrainfarction block would be summated to those produced by the LPSB

In the presence of posteroinferior myocardial infarction the broad QRS interval with a terminal slurred R wave as well as the terminal slurrings of the VCG has been attributed to peri infarction block [11 13] This conduction disturbance has been recorded in experimental posteroinferior necrosis by means of direct bipolar leads in our laboratory[4] and also by other investigators [14] However in this condition the delay was moderate and the manifestations of the mentioned block in peripheral leads were very small or unnoticeable [4] since the ventricular complexes in Leads III and aV_F were of Qrs type and not of QR type as should be expected according to Bayley s concept[11] of peri infarction block In this case the presence of S waves indicates that the subepicardial layer of muscular tissue explored was not the last to be activated [4] Only when LPSB was associated terminal R waves appeared in the leads mentioned above Due to these facts we think that in a posteroinferior myocardial infarction the terminal and slurred R waves with a delayed intrinsicoid deflection in Leads III and aV_F are due predominantly to an associated LPSB even in the presence of QRS intervals of less than 0 12 second

LPSB and right bundle branch block (RBBB) In isolated RBBB the delayed activation of the basal portion of the right ventricle can be represented by a vector directed forward and to the right pointing between +150 degrees and −170 degrees in the frontal plane originating the typical morphologies of rsR type in V_1 and qR or QR in aV_R The association of LPSB may shift the direction of this vector downward forward and less to the right disappearing or reducing the terminal R waves in aV_R

In the VCG the RBBB gives rise to an S loop mainly directed forward and to the right with its terminal portion slightly above the E point This terminal portion situated above the E point may be shifted partially below it by the LPSB (see Fig 6)

LPSB and left ventricular enlargement

When left precordial leads reflect potential variations of areas affected by the LPSB they can present high voltage R waves with delayed intrinsicoid deflection [15] which could suggest left ventricular enlargement However, if the ventricular complexes in those leads are similar to those of Leads III and aV_F, and slurrings, notches or plateaus etc , are observed, the diagnosis of LPSB can be suggested as in the case presented in Fig 6 Actually, in this case the chest films did not show any degree of left ventricular enlargement

In Fig 1 we may observe that when LPSB is present, deep S waves appear in the right precordial leads, which could also suggest left ventricular enlargement

In conclusion, LPSB can produce electrical signs suggesting left ventricular enlargement but the presence of other features of LPSB incline towards this diagnosis However, both entities may coexist as in the tracings of Fig 1 belonging to a patient with left ventricular enlargement

Conclusion

According to the experimental and clinical findings the following criteria for the diagnosis of LPSB in man can be established

Electrocardiographic data

1. qR or QR complexes in Leads III and aV_F with slurring and/or a notch in the downstroke of this wave
2. Intrinsicoid deflection in aV_F and often in V_5 and $V_6 > 45$ msec
3. QRS duration generally augmented but possibly within normal limits
4. These characteristics may be observed in Leads V_5 and V_6 especially in vertical hearts Moreover, deep S waves can be present in right precordial leads
5. Frequently the S_I Q_{III} pattern is observed
6. ÂQRS around +60 degrees (average) although it may be deviated to the right
7. When associated with RBBB, the ventricular complexes in aV_R may be of rS, QS or Qr type, in the presence of rsR in Leads V_1 and V_{3R}, besides the slurred R waves in aV_F and V_6

Vectorcardiographic data

below the X axis, with clockwis
tion

2. Counterclockwise rotation of th horizontal plane (*H*) (although vary depending on the ass pathology) most of the cur loop) is situated at the left an teriorly from the E point
3. Slurrings of the initial and te portions of the curve
4. When RBBB coexists the S loo acteristic of the latter may b torted by LPSB and shifted m and below the E point in the plane

Summary

Experimental findings previousl served in dogs demonstrated that bl the posterior subdivision of the left b branch of His (LPSB) delays the actu of the posterior portion of the fr ventricular wall and of the posterio tion of the interventricular septum gives rise to characteristic ECG and changes These observations perm recognition of LPSB in clinical tracin this paper a study of 17 clinical EC VCG records is presented

The main ECG characteristics of are qR or QR complexes in Leads II aV_F with slurring and/or a notch downstroke of the R sometimes a sl in the initial portion is also observed there is a delayed onset of the intrin deflection of the R wave in aV_F (msec) In vertical hearts the above fe are also observed in Leads V_5 and V_6 is generally situated in the fourth qu (between +90 degrees and 0 degree though it may be deviated to the right quently the S_I Q_{III} pattern is present

The most important VCG data clockwise rotation of the VCG frontal (*F*), counterclockwise rotation of the horizontal plane (*H*), and slurrings o initial and terminal portions of the cur the three planes

LPSB can diminish or mask the ECG VCG signs of a posteroinferior myoca infarction Based on experimental obs tions it was concluded that in a pos inferior infarction the presence of term and slurred R waves with a delayed intr

with QRS complexes of less than 0 12 sec ond is due predominantly to an associated LPSB rather than to peri infarction block. LPSB may diminish the manifestations of right bundle branch block in aV_R Nevertheless the rsR complexes persist in Lead V_1 while the signs of LPSB are recognizable in Leads III aV_F and V_6

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Experience with surgical management of primary infective endocarditis: A collected review of 139 patients

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Seattle, Wash.

In the recent past the only surgical treatment of infective endocarditis consisted of removing infected spleens,[1] excising peripheral mycotic aneurysms, and ligation of infected patent ductus arteriosus.[3] Kay and associates[4] (1961) introduced the modern era in the management of this disease by performing a debridement of the tricuspid valve and closure of the ventricular septal defect in the presence of active Candida endocarditis of the tricuspid valve. In 1965 Wallace and co-workers performed the first successful prosthetic valve replacement in the acute stage of bacterial endocarditis. Implanting a foreign body in an infected site and in the presence of acute inflammation is contrary to fundamental surgical principles in any other anatomic site. However, this presently is the only alternative in patients with infective endocarditis with progressive congestive heart failure. During recent years several reports[6-27] have appeared stressing the urgency of valvular repair or replacement once intractable heart failure begins in the course of infective endocarditis.

The purpose of this article is to assess the results of surgery in the treatment of primary infective endocarditis in 139 patients in an attempt to condition attitudes and formulate guidelines for surgical intervention.

Clinical material and definitions

Of 139 patients presented in this study, 115 were collected from the English literature[4-23]; only those reports were included which contained adequate data for evaluation. The remaining 24 patients were operated upon at the University of Washington Hospital from December, 1961, to July, 1971; of these, 13 have been reported on elsewhere.[20] Infection of the patent ductus arteriosus and ventricular septal defect are excluded from this study. For clarity, the term "primary" endocarditis refers to an infection of any inherent cardiac valve. "Secondary" endocarditis implies infection

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of the prosthetic or other biologic valves ie homo hetero or autologous valve The term infective endocarditis has been preferred to bacterial endocarditis so that infections by fungus and Rickettsia in addition to bacteria can be included

Residual infection is defined as a post operative infection of the prosthetic valve or the patient s own valve with the original organism while reinfection is due to a new organism

Classification Based on clinical features microscopic appearance and culture of the excised valve tissue these patients were retrospectively classified into two groups active and inactive or healed A patient was classified as active if any one of the following was observed in the excised valve (1) an acute inflammatory reaction micro scopically (2) organisms seen microscopically (3) organisms cultured from the valve (4) if septicemia was present at the time of the operation When none of these was present the patient was considered to be in the inactive or healed stage One hundred and five patients were operated upon during the active stage and 34 in the inactive or healed stage

Age and sex Table I shows the incidence of the disease in various decades of life in 30 patients the age was unstated There were 63 male and 23 female patients in the active stage and 17 male and 5 female subjects in the healed stage Sex was not mentioned in 31 patients The majority of patients with aortic valve endocarditis were between 21 and 50 years of age Mitral valve endocarditis was seen mostly in the 21 to-40-year age group and again in the group 51 to 60 years old

Pre-existent cardiac lesion Of 70 patients with known heart lesions before the onset of endocarditis 45 were in the active stage 19 in the healed stage in 6 patients with previous cardiac lesions the stage of the disease was undetermined Thirty six patients had no known pre existent cardiac lesion while in 29 patients this information was not available

Route of infection In the majority of patients this was either unknown or un stated In 48 patients where this information was available the portal of bacterial entry in the descending order of frequency was respiratory tract genitourinary tract and oral cavity Other routes of infection were infected hemodialysis A V shunt peritonitis from peritoneal dialysis intravenous drug abuse infected cut-down site and stab wound of the chest

Table I Age distribution

Age	*Cumulative series*		*U W series†*	
	Active	*Healed*	*Active*	*Healed*
0 to 10 years	—	—	2	—
11 to 20 years	6	4	—	1
21 to 30 years	15	7	3	2
31 to 40 years	18	2	5	3
41 to 50 years	16	2	4	1
51 to 60 years	11	—	1	2
61 to 70 years	5	—	—	—
Total	71	15	15	9

Det[illegible] bout [illegible] of d[illegible] [illegible] available in 29 patie[illegible]
†[illegible] ty of W[illegible]gton

Bacteriology Table II shows the various causative organisms As a group Streptococcus was the commonest organism followed by Staphylococcus Pneumococcus and Candida in that order Twelve patients (8 4 per cent) had no growth of bacteria on preoperative blood cultures

Of 97 patients with aortic valve endocarditis the causative organism was *Streptococcus viridans* in 25 *Staphylococcus aureus* in 19 Pneumococcus in 10 Enterococcus in 6 and miscellaneous organisms in 21 The remaining 16 patients had either no growth or the blood culture results were unknown Of 20 patients with mitral valve involvement the causative organism was *Streptococcus viridans* in 6 *Staphylococcus aureus* in 4 *Streptococcus hemolyticus* and *Streptococcus faecalis* in one each In 3 patients endocarditis was caused by miscellaneous organisms and the remaining patients had either no growth or the blood culture results were unknown Of 17 patients with combined aortic and mitral valve endocarditis the causative organism was *Streptococcus viridans* in 4 *Staphylococcus aureus* in 2 Candida in 2 and *Streptococcus hemolyticus* and *Streptococcus anaerobius* in 1 each The culture was either sterile or unknown in 7 patients

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61 to 70 years	5	—	—	—
Total	71	15	15	9

Details about stage of disease not available in 29 patients

† University of Washington

and oral cavity. Other routes of infection were infected hemodialysis A V shunt, peritonitis from peritoneal dialysis, intravenous drug abuse, infected cut-down site and stab wound of the chest.

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Table II. Bacteriology

Organism	*Active*		*Healed*		*Stage unknown*	
Streptococcus	33		13		10	
S. viridans		21		8		10
S. faecalis (Enterococcus)		7		1		0
S. hemolyticus		1		3		0
Others		4		1		0
Staphylococcus	22		6		3	
S. aureus		20		5		2
S. albus		2		1		1
Pneumococcus	9		0		4	
Klebsiella	1		0		1	
Neisseria perflava	1		0		0	
Paracolon	0		1		0	
Serratia marcescens	1		0		0	
Brucella suis Type III	1		0		0	
Candida	5		0		0	
C. albicans		3		0		0
C. krusei		1		0		0
C. parakrusei		1		0		0
Vibrio species	1		0		0	
Diptheroids	1		0		0	
Negative culture	10		0		2	
Unknown	9		3		2	
Total	94		23		22	

Table III. Indications for surgery

Indications	*Cumulative series**		*U. H. series*		*Total*
	Active	*Healed*	*Active*	*Healed*	
C.H.F.	70	24	10	6	110
C.H.F. + embolization	8	1	3	3	15
C.H.F. + resistant infection	3	—	1	—	4
C.H.F. + embolization and resistant infection	3	—	—	—	3
Embolization + resistant infection	1	—	—	—	1
Resistant infection/drug toxicity	3	—	1	—	4
				Total	137

C.H.F. = Congestive heart failure.
*In 2 patients operated upon for C.H.F. the stage of the disease was undetermined.

Indications for operation. Table III lists various indications for open heart surgery. Congestive heart failure alone or along with other conditions was the indication for surgery in 134 patients (96 per cent). Septic embolization alone or with other complications was encountered in 19 patients while resistant infection alone or with other conditions were seen in 12 patients.

Surgery. All patients were operated upon with the aid of cardiopulmonary bypass. In our own series of 24 patients a rotating disc oxygenator primed with a mixture of blood and lactated Ringer's solution was employed using a flow rate of 2.4 L. per square meter per minute.

Left heart valves (aortic and/or mitral valve) were involved in 135 patients while

Table IV. Valve involved

Valve	Cumulative series		U W series		Total
	Active	Healed	Active	Healed	
AV	66	19	10	2	97
MV	10	3	3	4	20
AV + MV	11	2	?	?	17
PV	1	—	—	—	1
TV	?	—	1	—	3
MV + TV	—	—	—	1	1
				Total	139

AV rtl l e MV = mitral val PV = pulm ic valve TV = tricuspid valv

Table V. Operative procedures

Procedure	Cumulative series		U W series		Total
	Active	Healed	Active	Healed	
AV					
Prosthetic valve repl	62	14	7	2	85
Homograft aortic valve repl	1	1	2	1	5
Autologous tissue valve repl	—	—	1	—	1
Repl with Bahnson leaflet	—	4	—	—	4
Repair SV aneurysm and/or fistula	8	1	2	1	12
Repair aorta PA fistula	1	—	—	—	1
MV					
Prosthetic valve repl	9	—	2	—	11
Reconstruction	1	3	1	4	9
AV + MV					
Prosthetic valve repl	5	2	1	—	8
Prosthetic AV repl. + MV reconstruction/débridement	6	—	0	1	7
TV					
Prosthetic valve repl	1	—	0	—	1
Débridement + annuloplasty	1	—	1	—	2
PV					
Débridement	1	—	0	—	1
MV + TV					
Prosthetic valve repl	—	—	—	1	1

AV = aortic alve MV = mitral valve PV = p lmo c valve TV = tricusp d val Repl. = replacem nt U W = U iversity f Washingto SV = si of Valsalva PA = pulm nary rtery
*Stage of disease co ld not be det rmined i 2 p tie ts and ne patie t died n the table before valve replaceme t

5 patients had involvement of the right heart valves (Table IV) Of 4 patients with tricuspid valve endocarditis 2 were drug addicts

Of 97 patients with aortic valve endocarditis 76 (77 per cent) were operated upon in the active stage and 21 were operated upon in the inactive or healed stage Of 20 patients with mitral valve infection 13 (65 per cent) were operated on in the active stage

The various operative procedures performed are listed in Table V In 24 patients operated upon at the University of Wash-

Table VI Pathologic findings

Findings	Cumulative series no of valves	U W series no of valves
Leaflet destruction and/or perforation and/or laceration	65	21
Vegetations or verrucae	55	6
Myocardial abscess and/or annular abscess and/or SVA	11	6
Sinus of Valsalva fistula	6	1
Ruptured chordae tendineae	12	8
Ventricular septal defect	1	—
Aorta—pulmonary artery fistula	1	—
Leaflet deformity and/or scarring and/or calcification	24	1

SVA = sinus of Valsalva aneurysm
*Details about perforation or vegetations not mentioned in 17 patients

Table VII Results

Series	Stage	No of patients	Early mortality rate (%)	Late mortality rate (%)	No of patients†	Regurgitation‡	Residual infection	Reinfection	Reoperation
Cumulative series	Active	90	22(24 4)	7	85	12	2	1	9§
	Healed	25	3(12)	1	25	5	—	—	2
U W series	Active	15	6	—	12	6	—	1	—
	Healed	9	1	1	8	2	—	—	—
		139	35(25)	9(8 6)	130	25	2	2	11

*Includes three deaths where the stage of disease was undetermined
†Number of patients who left the operating room
‡Seven patients with regurgitation murmurs are excluded as the stage of disease could not be determined
§Three patients were reoperated on for prosthetic valve malfunction

ington the mitral valve was salvaged whenever possible and mitral valve replacement was done when reconstructive procedures were not feasible[33] Also during 1965 to 1967 betapropiolactone sterilized aortic homografts were used for aortic valve replacement[34]

Table VI reveals the various pathologic findings observed at the time of surgery

Results

Table VII shows the results after cardiac surgery in endocarditis The over all early mortality rate (death within 30 days of operation) was 25 per cent The early mortality rate in the active and healed stage was 26 6 and 11 7 per cent, respectively, the actual early mortality rate is slightly higher than these figures because it was not possible to ascertain the stage of disease in 3 early deaths One hundred and four patients were followed from one month to 8 years There were 9 (8 6 per cent) late deaths (death after 30 days of operation) Causes of early and late deaths are listed in Table VIII Table IX correlates the results with the valve involved

Recurrent regurgitation and reoperation Of 130 patients who left the operating room 32 (25 per cent) patients developed murmurs of regurgitation (Table VII) The exact incidence of this complication is probably higher than 25 per cent because in many reports precise information was not available Of 32 patients 3 (9 per cent) died of congestive heart failure and/or septicemia and 9 (33 per cent) were reoperated upon (two were reoperated upon twice) Of six patients who survived the reoperation two have murmurs of regurgitation Twenty patients who have murmurs of regurgitation are compensated and are

Table VIII Causes of death

Early deaths (less than 30 days after operation)		Late deaths (more than 30 days after operation)	
Cause	*No*	*Cause*	*No*
C H F with unresponsive myocardium	7	C H F due to recurrent regurgitation	4
Septicemia	5	Septicemia † emboli and C H F	1
Arrhythmias	4	Disruption aortic wall suture line	1
Pulmonary emboli	2	Pneumonia and recurrent lung cancer	1
Miscellaneous causes	12	Clotted prosthetic valve (with infected thrombus) and septicemia‡	1
Unknown causes	5		
Total	35	Total	8

C H F = c g st he rt 1 lure
*Septice ia d to re t t g em 3 pat ts.
†Organ sm C d d lb s
Organ sm a *Bruc ll* Type III

Table IX Results according to the valve involved

Valves involved	*No of patients*	*Early mortality rate (%)*	*Late mortality rate (%)*	*Regurgitation*	
				Not reoperated	*Reoperated*
AV	80	19 (24)	((11 5)	8	5
MV	13	3 (23)	0	5	0
AV + MV	14	3 (21)	1 (10)	?	2
TV	3	—	—	1	—
PV	1	—	—	1	—
MV + TV	1	1	—	—	—

AV t l MV = mit al al TV = tri usp d l PV = p lm c val
De d we t va'lable 27 pat e t

without significant symptoms Three patients were reoperated upon because of prosthetic valve malfunction one had ball valve variance and 2 had failure of a Hufnagel Silastic leaflet

Residual infection and reinfection Two patients evidenced residual infection by *Brucella suis* Type III and *Candida albicans* respectively (Table VIII) The first died of occlusion of the ball valve prosthesis with an infected thrombus while the other (who was reoperated upon once) died due to recurrent regurgitation/septicemia Two patients developed reinfection One had staphylococcal septicemia with involvement of the mitral valve and died the aortic valve prosthesis was not involved The other patient developed enterococcal reinfection and as a result has *moderate* aortic regurgitation

Four patients died in the early postoperative period because of septicemia due to infection with *Pseudomonas aeruginosa* and Aerobacter Candida coliform organism and *Pseudomonas aeruginosa* respectively none of these was reported to have vegetations on the prosthesis at autopsy Table X correlates the preoperative antibiotic therapy with the postoperative results

Valve culture Valve cultures were available for 50 patients No organism was grown on valve culture in 37 patients while 13 patients had a positive valve culture Of 13 5 patients had the same organism as in preoperative blood culture while 7 patients grew different organisms Microscopic ex

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U W series	Active	15	6	—	12	6	—	1	2
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*Includes three deaths in which the stage of disease was undetermined
†Number of patients who left the operating room
‡Seven patients with regurgitation murmurs are excluded as the stage of disease could not be determined
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Table VI reveals the various pathologic findings observed at the time of surgery

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particularly those with aortic valve involvement (see text below) may deteriorate rapidly. An aggressive attitude with regard to early surgical intervention, particularly in aortic valve endocarditis and regurgitation, is essential in order to avoid unnecessary delay and reduce the early postoperative mortality.

Whether unoperated aortic valve infection carries a worse prognosis than mitral valve infection is controversial. Cohen and Freedman[17] reported a 54 per cent mortality rate in patients with aortic regurgitation developed during the course of endocarditis compared with a 28 per cent mortality rate in patients with other valvular lesions. Tompsett and Lubash[13] regarded the development of aortic regurgitation and congestive heart failure to be an ominous sign. Lerner and Weinstein[39] on the other hand suggested that poor prognosis in aortic valve infection was not due to the aortic valve per se but because of its increased incidence in elderly men with associated arteriosclerosis and causative organisms of greater invasiveness. Even though the mitral valve has been reported to be the commonest site of infection in the literature,[35] the majority (89 per cent) of patients who needed surgery on an urgent or semiurgent basis in the authors' series had aortic valve endocarditis. Prognostically this means that the aortic valve is an unfavorable site because most patients either will die or require surgery. This suggests that acute aortic regurgitation is more poorly tolerated than acute mitral regurgitation.[40]

Adequate preoperative antibiotic therapy is important. Ideally antibiotics should be given for 3 to 4 weeks in streptococcal endocarditis and for 6 to 8 weeks in staphylococcal endocarditis.[41] When progressive heart failure starts, however, surgery should not be delayed in attempts to eradicate the infection in order to forestall residual infection of the prosthetic valve.[42] It appears from the author's series that residual infection has not been a major problem (Table VII): only 2 of 130 patients (1.6 per cent) who left the operating room exhibited residual infection despite the fact that 13 patients (10 per cent) had positive valve culture. While organisms were seen microscopically in the excised valve in 23 patients only two had a positive valve culture. This suggests that even when a full course of antibiotic therapy has not been given the valve was rendered sterile in a number of patients (Table X). Duration of postoperative antibiotic therapy is governed by the adequacy of the preoperative antibiotic course and the culture report of the excised valve. Because of concern about reinfection with resistant organisms the authors avoided a prolonged postoperative antibiotic therapy and administered antibiotics for 5 to 10 days only.[30]

The major postoperative complication has been recurrent regurgitation. This was observed frequently when surgery was undertaken in the acute stage. Except for one patient (who had Candida endocarditis) this has not been related to infection but related to the edematous and friable tissue with poor suture holding power. In the majority of patients the regurgitation has not been significant and only a few patients have required reoperation. Because of recurrent regurgitation special attention should be paid to insertion of sutures in the friable annulus. Neville and co-workers[26] recommend passing buttressed mattress sutures from the outside through the aortic wall and the prosthesis sewing ring. Hatcher and associates[18] reported the excision of the infected aortic valve as well as the adjoining aortic wall which was the seat of infection and abscess formation with the replacement of the aortic valve with a prosthetic valve and reconstruction of the ascending aorta with a Teflon tube graft in 2 patients.

Increase in intravenous drug abuse in recent years has led to a higher incidence of tricuspid valve endocarditis.[43] Management of endocarditis in hardened drug addicts is a difficult problem because of increased chances of reinfection if prosthetic valvular replacement is done. Recently total tricuspid valve excision without replacement with a prosthetic valve has been reported with good results.[44] Tricuspid regurgitation seems to be well tolerated if the pulmonic valve is competent and if there is no pulmonary hypertension.

Summary

One hundred thirty-nine patients with primary infective endocarditis who underwent open heart surgery are analyzed of

Table X. Preoperative antibiotic therapy, bacteriology of the excised valve, and results

Duration of preoperative antibiotics	No. of patients*	Positive valve culture	Negative valve culture	Organism seen microscopically with negative valve culture	Early mortality (%)	Late mortality	Residual infection	Reinfection	Regurgitation		
									Reoperated	Not reoperated	Not mentioned
0 to 10 days	8	1†	4	6	2‖ (25)	—	—	—	2	—	—
11 to 20 days	14	2‡	7	4	5¶ (35)	—	—	1	1 (×2)	—	4
21 to 40 days	15	3†	7	5	3# (20)	1**	—	—	4	2	1
More than 40 days	17	7§	9	2	3 (18)	—	1	1	—	5	4

*Only 54 patients in whom complete information was available were analyzed.
†Organism cultured was different from preoperative blood culture.
‡Organism cultured was same as on preoperative blood culture.
§Organism cultured was same as on preoperative blood culture in 3 patients and different in 4 patients.
‖One patient died following reoperation for recurrent regurgitation.
¶One patient developed staphylococcal endocarditis of the mitral valve and septicemia.
#One patient died of candidiasis.
**Died after reoperation for regurgitation (due to residual infection with Candida).

amination of the excised valve showed organisms in 23 patients, of these only 2 had positive culture.

Discussion

In the preantibiotic era, most patients who suffered from infective endocarditis died of septicemia. Now because of our ability to control infection, a very prominent feature of this disease, viz. heart failure, was unmasked. Robinson and Ruedy[35] observed that 61 per cent of deaths in the postantibiotic period are due to congestive heart failure compared to 6 per cent in the preantibiotic era. This increased incidence of congestive heart failure they attribute to the increased frequency of valvular perforations and tears because myocardial changes could not be correlated.

The onset of congestive heart failure during the course of infective endocarditis is generally regarded to carry a grave prognosis. Before the availability of open heart surgery, 97 per cent of patients with infective endocarditis died when severe congestive heart failure was present before antibiotic therapy was started, while 79 to 89 per cent of patients succumbed who developed heart failure during antibiotic treatment.[36] The relatively low overall mortality rate in 139 patients in the present series highlights the tremendous impact cardiac surgery has made on this disease. Next to antibiotics, introduction of open heart surgery in the management of infective endocarditis has been the most significant recent advance in changing the prognosis of an entity which was almost uniformly fatal.

The proper timing of surgery is critical in the treatment of infective endocarditis. While it is obviously desirable to have a sterile blood stream and sterile valve tissue, it cannot be overemphasized that the hemodynamic status of the patient is the ultimate determinant of the timing of operation. Procrastination in order to achieve bacteriologic sterilization or control congestive heart failure with digitalis and diuretic therapy often causes loss of precious time and leads to irreversible myocardial damage. Indeed the commonest cause of early death in the present series was a myocardium which could not maintain cardiac output at the termination of cardiopulmonary bypass (Table VIII). Once congestive heart failure starts due to perforation or tear of a valve leaflet the course of disease is difficult to predict. Some patients will stabilize while others and

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3 Oliver J E Williams T W Howell J F Crawford E S Morris G C and De Bakey M E Valvular replacement in bacterial endocarditis Cardiovasc Res Cent Bull 8 126 1970
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these 24 patients were operated upon at the University of Washington while the rest have been collected from the English literature. One hundred five patients were operated during the active stage and 34 patients in the healed stage. Seventy patients had pre-existent cardiac lesions before the onset of endocarditis. As a group, Streptococcus was the commonest infective organism followed by Staphylococcus. Congestive heart failure alone or with other conditions was the indication for surgery in 96 per cent of patients. Left heart valves were involved in 135 patients, the aortic valve being the commonest site of infection. Prosthetic valve replacement alone or along with other procedures was done in 113 patients; in the remaining patients reconstructive procedures or homograft valve replacement was done.

Over-all early and late mortality rates in the entire series were 25 and 8.6 per cent, respectively. The early mortality rate in the active stage was about 26.6 per cent while in the healed stage it was 11.7 per cent. Of 130 patients who left the operating room, 32 were reported to develop murmurs of regurgitation; of these 32 patients, 3 died of congestive heart failure and/or septicemia, 9 were reoperated upon, while the rest are stable. Two patients had residual infection with the original organism while another 2 patients developed reinfection with a new organism.

Hemodynamic status is the most important determinant of timing of the operation in this disease. Once congestive heart failure starts due to tear or perforation of a leaflet during the course of active endocarditis, particularly of the aortic valve, surgery should be undertaken at an early date. It is suggested that an aggressive attitude with regard to early surgical intervention in these patients should further reduce the early mortality rate.

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Results

When first seen the tachycardia was of sustained nature in 7 patients and repetitive in 9 The clinical electrocardiographic and therapeutic features of the two groups will be discussed separately

1 *Clinical course* (Table I)

(A) SUSTAINED TACHYCARDIA (7 patients) There were 3 girls and 4 boys in this group The age range at onset extended from 2 weeks to 12 years (median age 5 years) General symptoms were non specific but 4 had congestive heart failure with significant cardiac enlargement at the initial visit and another 1 (D W) to be presented in detail developed congestive cardiac failure a year after he was first seen At the end of the follow up period which ranged from 8 years to 16 years (median 10 years) all patients but one are alive and are essentially asymptomatic Five (S L K B T P D W and D Z) are in normal sinus rhythm 3 of them without any medications 1 (D W) is still on digitalis and reserpine and the fifth patient (D Z) continues to have brief episodes of tachycardia lasting one to two minutes approximately once per week but prefers this to taking medications The remaining patient (K L) now aged 8 years has sustained tachycardia at a rate of 140 and mild cardiac enlargement in spite of digitalis therapy At cardiac catheterization at age 2 years (6 years ago) she was in sustained tachycardia had mild mitral regurgitation a reduced ejection fraction and a left ventricular end diastolic pressure of 12 mm Hg

Further details are now presented on 2 patients one (R J) being our only fatality with an atypical course and the other (D W) representing the longest follow up in this group and also the only patient with neurological complications

R J At another hospital this boy presented with atrial tachycardia congestive cardiac failure and cardiomegaly at the age of 12 years Past medical history and family history were negative With digitalis therapy the initial ventricular rate of 200 slowed over a three month hospital course to 120 and cardiomegaly decreased At age 14 sinus rhythm was present cardiac size was radiologically at the upper limits of normal and digitalis was then discontinued He remained asymptomatic until age 19 when sustained tachycardia reappeared and persisted thereafter despite digitalis therapy At cardiac catheterization the following year mitral regurgitation was demonstrated at angiography and the left ventricular end diastolic pressure was 20 mm. Hg Cardiomegaly was considerable At age 21 while relatively asymptomatic he died in his sleep No autopsy was performed

D W This male patient now 23 years was presented in the previous report[2] Briefly sustained tachycardia was first noted at 5 years of age. At age 6 he was readmitted with sustained tachycardia in congestive heart failure and four days later developed a left hemiplegia Subsequently sustained tachycardia reappeared at ages 8 and 14 medications having been discontinued 13 months and 7 months previously respectively The third episode of tachycardia lasted 1 year Since then the patient has remained in normal sinus rhythm and continues to receive digitalis and reserpine There are no cardiac symptoms although a significant left hemiparesis moderate expressive dysphasia, and occasional seizures persist

(B) REPETITIVE TACHYCARDIA (9 patients) There were 3 girls and 6 boys in this group The age range when first seen extended from 6 days to 17 years (median age 5 years) All but 2 of the patients R W and J M were asymptomatic and the tachycardia was accidentally discovered One of the asymptomatic patients had infectious mononucleosis three months previously None had congestive heart failure or cardiac enlargement At the end of the follow up period ranging from 3 to 22 years (median 9 years) all the patients are alive and only R W is symptomatic Despite the excellent clinical course all but two patients (D M and R I) still have the repetitive arrhythmia Six patients are taking digitalis three of the six are also taking a second drug (propranolol reserpine and quinidine respectively)

Further details are now presented on 1 patient (R L) representing an example of return to normal sinus rhythm the

Chronic ectopic tachycardia of infancy and childhood

John F Keane, M D
William H Plauth, Jr, M D
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Paroxysmal tachycardia in young patients is not uncommon Keith Rowe and Vlad[1] estimated its occurrence at 1 in 25 000 children In its classical form it is characterized by abrupt onset and offset of rapid fixed regular rate infrequent recurrence, and prompt response to and satisfactory control by the usual medical management

There is however another group with characteristic electrocardiograms (ECG s) among the children with paroxysmal tachycardia (fortunately a much smaller one) in whom tachycardia is sustained or repetitive In these patients the over all slow rate varies with the state of consciousness posture respiration and vagal stimulation and the arrhythmia responds less satisfactorily to medical management and may persist for many years In 1964, a report on 10 patients with this type of chronic ectopic tachycardia was published from this institution, representing a 17 year experience It is the purpose of this current communication (1) to present a follow up of the original 10 patients (2) to describe an additional 6 patients seen since and (3) to comment on the possible mechanism as well as on the treatment of these tachycardias

Materials and methods

Between 1943 and 1971, 16 patients 10 boys and 6 girls seen at the Childrens Hospital Medical Center, have fulfilled the following criteria of chronic ectopic tachycardia

1 Variable rate per minute with an average of less than 180 seldom greater than 200
2 Identifiable P waves almost invariably with an abnormal frontal plane axis
3 Chronicity through years, either with sustained or repetitive pattern In the sustained form the abnormal mechanism prevails continually through months and years In the repetitive variety the abnormal mechanism is interspersed by varying periods of sinus rhythm Transition from one form to the other may occur
4 Resistance to conventional antiarrhythmic therapy

In all patients no other cardiac abnormality was evident

The clinical course of these patients is presented and their ECG s have been reviewed with particular reference to the criteria for reciprocating tachycardia as outlined by Gettes and Yoshonis[3] These

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4. Resistance to conventional antiarrhythmic therapy.

In all patients, no other cardiac abnormality was evident.

The clinical course of these patients is presented, and their ECG's have been reviewed with particular reference to the criteria for reciprocating tachycardia as outlined by Gettes and Yoshonis.[3] These

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Table IV Drugs used and response

Variables	Patient's initials	Digitalis	Quinidine	Procainamide	Reserpine	Propranolol
Sustained	S L.	+	+	0†	0	0
	K. L.	+	0	—‡	—	—
	K. B	+	—	—	—	0
	R. J	+	—	0	—	0
	D Z	+	+	0	0	0
	D W	+	—	0	+	0
	T P	+	—	0	0	0
Repetitive	G M	+	+	0	—	0
	V B	—	—	+	—	0
	J M	+	—	0	+	+
	L H	+	0	0	0	0
	R. L	+	—	—	+	0
	D M	+	0	0	0	0
	R. W	+	+	—	—	—
	J E	+	0	0	+	0
	J R	0	0	0	0	0

+ = administered, probably effective.
†0 = not administered.
‡— = administered, probably ineffective.

ventricular rate by one or more of the following methods In 5 patients it slowed the intrinsic ectopic rate and in 3 of these in addition it produced varying A V block (mainly 2 1) as shown in Fig 2 In the remaining 2 patients it converted the sustained rhythm to the repetitive variety (Fig 3) Congestive heart failure responded promptly in 4 of the 5 patients in whom it occurred while in the fifth it subsided gradually Among the group of 9 patients with repetitive tachycardia the glycoside was administered to 8 It produced slowing of the over all ventricular rate in 6 by reducing both the rate and frequency of the ectopic focus In a seventh patient R W whose paroxysms were longer and sometimes separated by minutes it reduced the number of symptomatic paroxysms and it was without effect in the eighth patient

QUINIDINE This was administered in addition to digitalis to 11 patients Among the 6 patients in the sustained group quinidine was effective in 2 In patient S L. it converted the digitalis induced repetitive tachycardia to normal sinus rhythm When medication were discontinued on 2 occasions sustained tachycardia recurred albeit several months later and normal sinus mechanism was again restored in similar fashion In patient D Z the sustained tachycardia present since age 9 was treated with digitalization with the appearance of 2 1 A V block 3 years later it converted to normal sinus rhythm He remained asymptomatic until age 13 when in spite of continued digitalis therapy he began to experience daily episodes of tachycardia often provoked by exertion and accompanied by angina and even syncope on a few occasions His attacks gradually decreased in frequency with the addition of quinidine his symptoms ceased and since age 18 without medication he has been asymptomatic and in normal sinus rhythm with only very brief occasional episodes of tachycardia In the remaining 4 patients in this group the drug was ineffective Quinidine reduced the ventricular rate in one patient (G M) among the repetitive group by markedly reducing the number of ectopic beats The drug reduced

Table II ECG features

Variables	Patient No	Patient initials	At onset		When last seen	
			V rate*	Ectopic P wave axis	V rate*	Ectopic P wave axis
Sustained	1	S L	200	Superior	56	NSR
	2	K L	280	Superior	140	Superior
	3	K B	220	Superior	62	NSR
	4	R J	220	Superior	120	Superio
	5	D Z	220	+110	80	NSR
	6	D W	200	+135	80	NSR
	7	T P	240	+75	85	NSR
Repetitive	8	G M	140 (atrial rate = 100)	+75	100	+75
	9	V B	140	Superior	130	Superior
	10	J M	170	+135	58	+135
	11	I H	100	Superior	100	Superior
	12	R L	150	Superior	70	NSR
	13	D M	260	Superior	7?	NSR
	14	R W	220	Superior	80	Superior
	15	J E	140	Superior	118	Superior
	16	J R	120	Superior	85	Superior

*Abbreviations V = ventricular NSR = normal sinus rhythm

*Table III Reciprocating rhythm criteria**

Variables			Criteria						
			A	B	C	D (additional criteria)			
Patient No	Patient's initials	Sex	Tachycardia recurring within minutes of termination	Onset following prolongation of P R or R P interval	Superior P of tachycardia (different from P at onset)	Atrial echoes	Termination with both P and QRS complex	Presence of retrograde P same as in tachycardia	Resetting of tachycardia by PVC†
1	S L	F	+	+	+	+	+	0	0
2	K B	F	+	+	+	+	+	0	0
3	V B	F	+	+	+	+	0	0	0
4	K L	F	+	+ +	+	0	0	0	+
5	R L	M	+	+	+	+	+	0	0
6	D M	M	+	+	+	0	+	0	0
7	R W	M	+	+	+	+	+	+	0
8	J E	M	+	+	+	+	0	0	0
9	L H	M	+	+	+	+	+	0	0
10	J R	M	+	+	+	0	+	0	0
11	R J	M	Died at age ?1 years Onset and termination of tachycardia not recorded						

*To suspect reciprocating rhythm items A B C and at least one element under D are necessary
†PVC = premature ventricular contraction

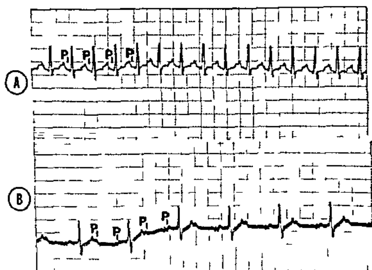


Fig 2 *A* and *B* Slowing of ventricular rate with 2 1 A V block due to digitalis *A* shows initial rate 200 per minute *B* illustrates 2 1 A V block atrial rate reduced to 170 per minute and ventricular rate 85 per minute

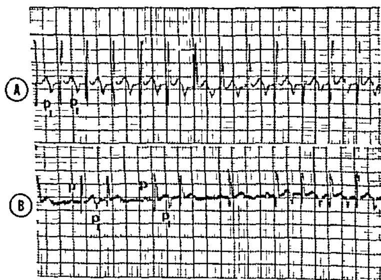


Fig 3 *A* and *B* Conversion of sustained form of tachycardia to repetitive form by digitalis both Lead *II* tracings. *A* shows sustained tachycardia with superior P axis *B* illustrates repetitive tachycardia

others such as Williams[9] in 1835 In 1922 Louis Gallavardin[8, 10] described an atypical form mentioned auricular and ventricular varieties and insisted on distinguishing this from ordinary paroxysmal tachycardia In 1924 he termed this tachycardie en salves [11] In 1947 Parkinson and Papp[12] introduced the name repetitive to describe this type of tachycardia also mentioning atrial nodal and ventricular forms They stated that this type was characterized by short runs of tachycardia almost constantly present for months or years and only occasionally interrupted by normal sinus rhythm They also described a variety which was persistent later stressed by Schachnow Spellman and Rubin[13] and by Hay and Keidan [15] and which we refer to as sustained the tachycardia being constantly present for months or years without

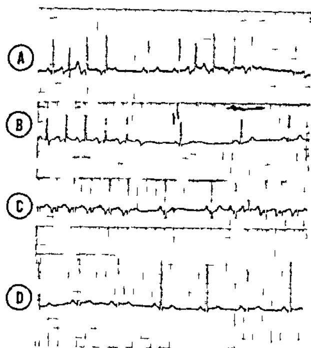


Fig. 1. *A* through *D*. All Lead 2 tracings showing reciprocating rhythm features in patient R. L. *A*. Demonstrates repetitive nature, initiation with sinus impulse (P waves nos. 1 and 6), increase in R-P' interval (following beats nos. 2 and 8), and termination with QRS (beats nos. 4 and 10). *B*. Shows termination of arrhythmia with superior P wave (following fifth QRS). *C* shows atrial echo beat following seventh QRS complex. *D* illustrates normal sinus rhythm after 12 years.

the number of symptomatic paroxysms in one patient (R. W.), was of questionable benefit in another one (R. L.), and was felt to be of no value in the remaining 2.

PROCAINAMIDE. This drug was administered in addition to digitalis to 5 patients. In neither of the patients with sustained tachycardia was it effective. Among the 3 patients with repetitive tachycardia, procainamide was beneficial in only one (V. B.). In this 3 year old patient large doses (consisting of 1,875 mg. per day in divided doses) substantially reduced ectopic activity. During the subsequent 7 years a similar high dosage level was necessary to maintain this degree of effectiveness. At age 10 years because of the potential hazards involved in high dosage long-term administration of procainamide and the increasing prevalence of sinus mechanism, the drug was discontinued together with digitalis. When seen recently she had a brief episode of ectopic tachycardia which could be easily broken by a vagal maneuver and sinus rhythm persisted during her office visit.

RESERPINE. This was given, in addition to digitalis, to 4 in the sustained group and 6 in the repetitive group. In patient D. W. in the sustained group, normal sinus rhythm appeared after 13 months of treatment. On 2 subsequent occasions sustained tachycardia reappeared several months after cessation of all medication and normal sinus mechanism was restored 7 and 13 months, respectively, after resumption of both digitalis and reserpine. In a second patient, the drug was of questionable benefit, while in the remaining 2 patients the ventricular rate remained unchanged. Among the repetitive group, reserpine slowed the ventricular rate by reducing the frequency of the ectopic mechanisms in 2 patients. In a third patient (R. L.) reduction of the ventricular rate occurred at first and eventually, 12 years later, still on digitalis and reserpine, sinus rhythm appeared. In the remaining 3 patients, the drug was felt to be of no value.

PROPRANOLOL. This was given, in addition to digitalis, to only 3 patients. In patient K. F. with the sustained type, it was administered at age 7 years in increasing doses to a maximum level of 90 mg. per day for a total of 9 days without any beneficial effect. It was given to 2 patients among the repetitive group. In J. M. at age 15, a dosage of 40 mg. per day was ineffective. Dosage was gradually increased through the years to a level of 160 mg. per day at age 18. When seen at age 19 ectopic activity was markedly reduced. In patient R. W. at age 9 years, 30 mg. per day for 12 days resulted in a resting ventricular rate with normal sinus rhythm of 56 per minute. This was thought to be a dangerously slow rate and the drug was discontinued.

In one patient, J. R., no drugs have been used. Frequent ectopic beats have been present, both alone and in pairs, without change for 6 years. He continues to remain totally asymptomatic.

Discussion

In 1889 classical paroxysmal tachycardia was termed "la tachycardie essentielle paroxystique" by Bouveret,[7] the clinical picture having been previously described by

One boy patient with evidence of cardiomegaly mitral regurgitation and elevated left ventricular end-diastolic pressure died suddenly at age 21 Fifteen patients are alive 13 being asymptomatic one experiences chest pain and dizziness associated with runs of tachycardia and another has brief light headedness during short attacks One patient has a left hemiparesis which appeared at age 6 years during a sustained episode of tachycardia One asymptomatic patient has mild mitral regurgitation with cardiac catheterization evidence of impaired left ventricular function

Analysis of the ECGs showed the arrhythmia to be of supraventricular origin in 15 patients The sixteenth patient was felt to have a nodal tachycardia with aberrant ventricular conduction The arrhythmia in 10 patients was suspected to be a reciprocating rhythm

Therapy on the whole was rather unsatisfactory Among the wide variety of antiarrhythmic agents employed the most useful was digitalis

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evidence of sinus activity. They felt that this form did not differ greatly from the repetitive variety as it could be transformed with digitalis under hospital observation, at least temporarily, to the repetitive type.

This type of arrhythmia is quite rare and the few large series in the literature are composed predominantly of adults.[12, 14] Some small series of children have been reported[4, 15, 16] including a series of 10 patients presented from this institution in 1964.[2] Since that time an additional 6 patients have been seen by us.

Although the majority of our patients tolerated their ectopic rhythm without significant symptoms, 5 of 7 with sustained tachycardia developed congestive heart failure. It is interesting to note that left ventricular myocardial dysfunction, in terms of increased end-diastolic pressure and reduced ejection fraction, was noted in the 2 patients catheterized. Whether the decreased myocardial performance is a consequence of chronic arrhythmia or should be regarded as a manifestation of myopathy[17] underlying the arrhythmia, is difficult to decide. One patient had a cerebrovascular accident, similar to the one described by Schachnow, Spellman, and Rubin.[18] It may be of significance that this occurred during an attempt to convert with digitalis a siege of sustained tachycardia associated with congestive heart failure. The one boy with sustained tachycardia who subsequently died has been discussed already in detail.

Among the patients with sustained tachycardia, 5 of 7 eventually reverted to normal sinus rhythm after several years, irrespective of medication. By contrast, in children with repetitive tachycardia, the arrrhythmia seems more persistent. At the end of follow-up, only 2 of 9 patients were in normal sinus rhythm.

Analysis of the ECG's has been quite interesting. Despite the increased incidence of arrhythmias among patients with the Wolff-Parkinson-White syndrome, none in our group exhibited any of the characteristics of this entity. The arrhythmia was definitely supraventricular in 15 patients and probably also in the sixteenth. This is similar to the recent report of Levine and Smith,[14] who found convincing evidence for a ventricular origin in only 2 of 38 of their own adult patients with repetitive tachycardia. Twenty-nine of 40 patients, in contrast, mostly adults, in Cass's[12] review article which contained only 2 personally observed cases, were felt to have ventricular arrhythmias.

Bigger and Goldreyer[19] studying 6 adults with recurrent paroxysmal tachycardia by elaborate catheterization techniques found strong evidence that these indeed represented reciprocating rhythms. In a later study,[20] these same authors demonstrated that the arrhythmia was precipitated by an atrial premature depolarization. They concluded from their observations that supraventricular tachycardia is most often due to re-entry utilizing the A-V conducting system. While our material supports the thesis that many of these patients with chronic atrial tachycardia indeed have a reciprocating rhythm, the precipitating impulse in our children was of sinus origin rather than an atrial premature beat in all but one instance.

While therapy was less than completely effective in most patients, it was by no means totally unsatisfactory. Digitalis was of value in slowing the ventricular rate by one means or another, in all but one patient. All the other drugs were used in conjunction with digitalis. An occasional favorable therapeutic response was noted with quinidine, reserpine, and propranolol, while procainamide was definitely effective in only one patient. We could not predict who would and who would not respond to what drug, except for the uniformly favorable effect of digitalis. Also, if a patient responded adequately to one type of regimen once, he was likely to react the same way at a later administration. All through the long follow-up of these patients we were repeatedly impressed by the chronicity of the arrhythmia and were later uncertain whether any changes in rhythm were due to natural evolution or to any particular therapeutic steps taken.

Summary

Since 1943, 16 patients, 10 boys and 6 girls, with chronic ectopic tachycardia have been seen at the Children's Hospital Medical Center and have been followed for periods ranging from 3 to 22 years (median 10 years).

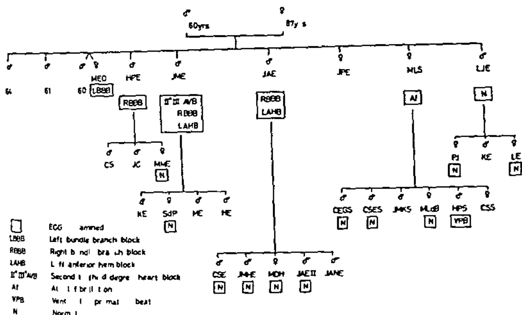


Fig 1 Family tree See text for particulars

ECG shows occasional unifocal ventricular premature beats but he is presently considered to be free of heart disease

Case C S E This 28-year old man is the eldest son of J A E. On account of his ECG and in the context of his family history he was carefully scrutinized for heart disease Apart from the abnormal ECG no such disease could be detected and although marked as normal in Fig 1 his ECG is considered to be an example of isolated left posterior hemiblock (LPHB)[3, 15]

Discussion

Simonsen[2] noted that hereditary block need not necessarily be congenital meaning that it need not cause disease at an early age In fact even the absence of conduction tissue need not present with symptoms until adult life[15] Because of the presence of 5 cases with intraventricular conduction disturbances in this family it is believed to be based on hereditary factors It is accepted that a group of patients exist in whom RBBB and LAHB progress to higher degrees of atrioventricular block in the absence of other manifestations of heart disease[16] It is interesting that in the present family we have a combination of these different degrees of intraventricular conduction disturbances

It was shown by Rosenbaum and associates[5] in a single patient that there could be interchan... trifascicular blocks and eventual progression to complete heart block On this premise it is tempting to assume that cases H P E and J M E may have developed their complete trifascicular blocks over the years however no proof of such progression exists in these cases because of the lack of serial ECG tracings The presence of RBBB and LAHB in the ECG of case J M E both before and after the occurrence of complete heart block would seem to invalidate the concept of a progressive trifascicular disease On the other hand it may strengthen the proposal made by James and Sherf[17] that the complete heart block may actually be caused by a disruption in internodal conducting pathways However it seems to us a rather wide anatomical area in which to locate the underlying pathological process and it could be argued that the distal focus for initiation of intraventricular conduction after the occurrence of complete heart block is in the left posterior division resulting in the ECG pattern of RBBB with LAHB[15] especially since it appears as if the left posterior division has the fastest rate of repolarization which makes it the most likely focus of distal impulse initiation[19] It should prove interesting to follow cases M E.O J A E and C S E in view of the possibility of the

Familial trifascicular block

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Although it is well known that heart diseases do occur in families the existing literature refers mostly to diseases other than arrhythmias. Certainly the familial occurrence of arrhythmias has been noted and includes cases of bundle branch block,[1] complete heart block,[2,3] and atrioventricular dissociation.[4,5] However, to our knowledge specific reference to familial trifascicular block is rare but incidental cases are to be found in published material. In a paper by Isagirris, Bustamante, and Friesendorff[6] electrocardiographic tracings can be recognized as having the features of trifascicular block. Other arrhythmias occurred in other members of this family. Gazes and associates[7] give a description of the electrocardiogram (ECG) of a patient with right bundle branch block (RBBB) and left axis deviation (−75 degrees) and despite the absence of a tracing it is presumed to represent a RBBB and left anterior hemiblock (LAHB).

It is the purpose of this communication to present a family with conduction disturbances involving the three fascicles of the bundle branches. The criteria used for ECG interpretation are those described by Rosenbaum and co-workers[8-10] and by others.[11-13]

Case studies

The family to be described here is of Caucasian South African extraction with no known consanguinity. As indicated in Fig. 1, the ECG's of 17 members of the family could be obtained. Of these 6 show some form of rhythm or conduction disturbance. The particulars of ECG's and relevant disease histories are as follows.

Case M. E. O. She is the twin of a brother who died from some unspecified heart disease at the age of 60 years. Her ECG shows complete left bundle branch block (LBBB). The P-R interval is normal at 0.16 second.

Case H. P. E. The patient was not seen by us but he was treated at another hospital with a permanent pacemaker for complete heart block. He represents Case 1, Fig. 2 of another report.[14] Apparently he suffered two previous myocardial infarctions and after cardioversion for supraventricular tachycardia with aberrant conduction his ECG showed sinus rhythm with RBBB.

Case J. M. E. He was treated at the age of 60 years with an implanted pacemaker for Stokes-Adams attacks following complete heart block. His initial ECG shows heart block varying between Mobitz type II second degree block associated with P-R intervals of 0.22 second and complete heart block. The QRS configuration is that of RBBB and LAHB.

Case J. A. E. He was seen initially at the age of 58 years complaining of vague chest pain. No confirmatory clinical, biochemical, or other evidence for the diagnosis of ischemic heart disease could be found. The ECG shows RBBB and LAHB and the P-R interval is 0.18 second.

Case M. L. S. She has a long history of cardiac failure secondary to mitral incompetence. Calcification was fluoroscopically visible in the mitral cusps and her ECG showed atrial fibrillation with normal intraventricular conduction. Presumably her arrhythmia is based upon the presence of mitral incompetence.

Case H. P. S. He is the son of M. L. S. and his

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Fig. 1 Family tree. See text for particulars.

ECG shows occasional unifocal ventricular premature beats but he is presently considered to be free of heart disease.

Case C. S. E. This 28-year old man is the eldest son of J. A. E. On account of his ECG and in the context of his family history he was carefully scrutinized for heart disease. Apart from the abnormal ECG no such disease could be detected and although marked as normal in Fig. 1 his ECG is considered to be an example of isolated left posterior hemiblock (LPHB).[8, 11]

Discussion

Simonsen[2] noted that hereditary block need not necessarily be congenital, meaning that it need *not* cause disease at an early age. In fact even the absence of conduction tissue need not present with symptoms until adult life.[15] Because of the presence of 5 cases with intraventricular conduction disturbances in this family, it is believed to be based on hereditary factors. It is accepted that a group of patients exist in whom RBBB and LAHB progress to higher degrees of atrioventricular block in the absence of other manifestations of heart disease.[16] It is interesting that in the present family we have a combination of these different degrees of intraventricular conduction disturbances.

It was shown by Rosenbaum and associates[8] in a single patient that there could be interchange of different trifascicular blocks and eventual progression to complete heart block. On this premise it is tempting to assume that cases H. P. E. and J. M. E. may have developed their complete trifascicular blocks over the years; however, no proof of such progression exists in these cases because of the lack of serial ECG tracings. The presence of RBBB and LAHB in the ECG of case J. M. E. both before and after the occurrence of complete heart block would seem to invalidate the concept of a progressive trifascicular disease. On the other hand, it may strengthen the proposal made by James and Sherf[17] that the complete heart block may actually be caused by a disruption in internodal conducting pathways. However, it seems to us a rather wide anatomical area in which to locate the underlying pathological process and it could be argued that the distal focus for initiation of intraventricular conduction after the occurrence of complete heart block is in the left posterior division, resulting in the ECG pattern of RBBB with LAHB,[15] especially since it appears as if the left posterior division has the fastest rate of repolarization, which makes it the most likely focus of distal impulse initiation.[18] It should prove interesting to follow cases M. E. O., J. A. E. and C. S. E. in view of the possibility of the

development of other types or higher degrees of trifascicular block

Isolated LPHB is quite rare[5,20] and even in combination with RBBB it is not of very frequent occurrence. This has been explained partly on the basis of blood supply but also on anatomical vulnerability to disease states.[1] However, it has been pointed out that the combination of RBBB and LPHB is more apt to develop into complete heart block.[21]

No proof exists of the underlying pathological cause of block in these cases. On statistical grounds it is most probably an idiopathic fibrosis in the region of the bundle branches and if this process be degenerative, then it is easy to visualize it as being progressive.

Summary

A family is presented in which different members have different types of intraventricular trifascicular blocks and it is speculated whether this might be a hereditary and progressive degenerative disease.

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Floating a catheter into the pulmonary artery in transposition of the great arteries

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In determining the suitability of a patient with D transposition of the great arteries for corrective surgery it is important to measure the pressure in the pulmonary artery and document the severity of any valvular or subpulmonary obstruction present Unfortunately this information is not easily obtained due to the technical difficulties of manipulating a catheter into the pulmonary artery Several techniques have been described in an attempt to overcome this problem[1-4] but these have lacked the simplicity required for general acceptance Recently Kelly Krovetz and Rowe[5] reported entering the pulmonary artery of two infants using a double lumen flotation catheter

This paper describes a simple technique for catheterization of the pulmonary artery in D transposition of the great arteries with an intact ventricular septum using a commercially available flow-directed catheter

Material

Twelve patients aged from 2½ months to 2 years were studied Their weights ranged from 5 4 kilograms to 10 4 kilograms (see Table 1) All had been catheterized previously in the newborn period at which time atrial septostomies had been created with a Rashkind balloon catheter The four smallest infants were recatheterized because of their poor progress two having clinical signs of anoxia The remaining eight cases were being evaluated as to their suitability for corrective surgery

Method

A number 5 French double lumen balloon catheter* is passed from either saphenous vein across the atrial septum into the left atrium where a loop is formed and advanced through the mitral valve into the left ventricle The balloon is then inflated in its position close to the mitral valve and is carried by the flow of blood into the pulmonary artery (Fig *1A*) This technique was used for the last ten catheterizations of this series the pulmonary artery being successfully entered in eight In two patients with large atrial chambers the atrial loop could not be formed because the tip of the catheter entered the left pulmonary veins repeatedly The pulmonary artery was subsequently entered using one of the methods described below

If the catheter is passed directly from the left atrium to the left ventricle without the formation of an atrial loop catheterization of the pulmonary artery is less success

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*Swan-Ganz flow-directed catheter Edwards Laboratories, Santa Ana, Calif

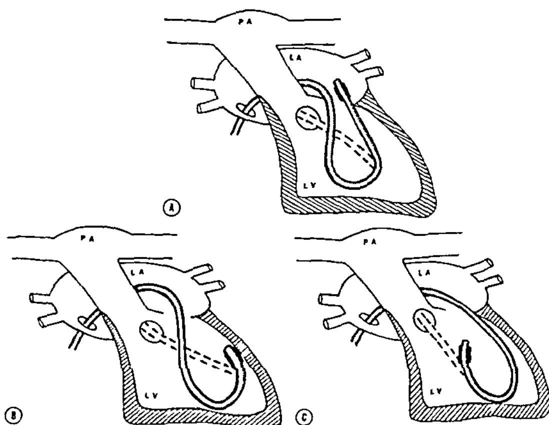


Fig 1 A through C Formation of the loop in catheterization of patients with TGA A The loop being formed through the mitral valve with the tip remaining just inside the left atrium Inflation of the balloon carries it into the left ventricle and out the pulmonary artery B and C Alternative loop formed in the left ventricle before inflation of the balloon *PA* = pulmonary artery *LA* = left atrium *LV* = left ventricle

Table I Weight, age and pressure gradient in twelve infants with transposition of the great arteries and an intact ventricular septum

Patient No	*Weight (Kg)*	*Age (mo)*	*Valvular or sub pulmonary gradient (mm Hg)*
1	5 4	7 5	36
2	5 5	13	26
3	5 ı	2 5	14
4	6 0	12	60
5	6 2	7	10
6	7 0	11	12
7	8 2	16	20
8	8 2	11	—
9	8 6	19	—
10	9 0	14	—
11	10 0	20	35
12	10 4	24	—

ful Inflation of the balloon with the tip just across the mitral valve resulted in catheterization of the pulmonary artery in only 40 per cent of our patients The alternative method of forming a loop in the distal part of the catheter by manipulation of its tip against the lateral or inferior left ventricular wall is technically more difficult and requires considerable manipulation of the catheter However once the loop is formed inflation of the balloon usually carries the catheter into the pulmonary artery (Figs *1B* and *1C*) Although short runs of premature ventricular contractions occurred when the catheter tip was being manipulated against the left ven ular wall only

an occasional premature ventricular contraction was noted while the balloon was inflated A similar low incidence of arrhythmias was reported by Swan and associates[6] in their series of right heart catheterizations in adults

It is recommended that the balloon be inflated with 0 5 c c of carbon dioxide which avoids the risk of air embolism should rupture occur A disadvantage of using carbon dioxide is that it diffuses through the wall of the latex balloon and reinflation may be necessary if there is undue delay in entering the pulmonary artery Pulmonary artery wedge pressures are obtained by reinflation of the balloon with a smaller quantity of gas when the catheter is positioned in a peripheral branch of the pulmonary artery

Results

The pulmonary artery was successfully catheterized in twelve successive patients with D transposition of the great arteries and an intact ventricular septum There were no patients in whom the technique was attempted but in whom it failed

The right pulmonary artery was easily entered in all cases and in five patients in whom wedge pressures were recorded satisfactory values were obtained The left pulmonary artery was entered in only one patient since with the inflation of the balloon in the main pulmonary artery the tip of the catheter was repeatedly carried into the right branch The pressure tracings obtained had good definition (Fig 2) and blood samples were withdrawn easily for analysis of oxygen saturation

In each patient the pulmonary artery was entered at least twice In two infants with subpulmonary gradients of 20 mm Hg and 35 mm Hg respectively repeated entry permitted a challenge of the obstruction with an Isuprel infusion systemic to pulmonary flow ratios being obtained at rest and during the infusion

The technique described is particularly advantageous in permitting data to be obtained from the pulmonary artery its branches and the wedge position In addition repeated entry of the pulmonary artery enables more sophisticated hemodynamic studies to be undertaken

In those patients with significant valvular or subpulmonary obstruction no additional difficulty was encountered entering the pulmonary artery Manipulation of the catheter was well tolerated and no complication occurred

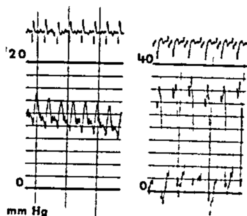


Fig 2 Representative pressure tracings recorded from the right pulmonary artery and left ventricle of two patients

Addendum

Three more infants have been studied since this paper was submitted for publication The two smallest (5 0 kilograms and 5 9 kilograms) were catheterized because of anoxic spells and had subpulmonary gradients of 30 mm Hg and 54 mm Hg respectively The third patient (6 6 kilograms) had no subpulmonary obstruction

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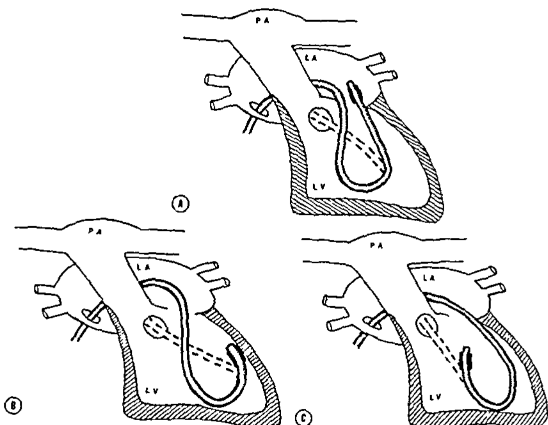


Fig. 1. A through C. Formation of the loop in catheterization of patients with TGA. A, The loop bein formed through the mitral valve with the tip remaining just inside the left atrium. Inflation of the balloon carries it into the left ventricle and out the pulmonary artery. B and C, Alternative loops formed in the left ventricle before inflation of the balloon. PA = pulmonary artery; LA = left atrium; LV = left ventricle.

Table I. Weight, age, and pressure gradient in twelve infants with transposition of the great arteries and an intact ventricular septum

Patient No.	*Weight (Kg.)*	*Age (mo.)*	*Valvular or subpulmonary gradient (mm. Hg)*
1	5.4	7.5	36
2	5.5	13	26
3	5.7	2.5	14
4	6.0	12	60
5	6.2	7	10
6	7.0	11	12
7	8.2	16	20
8	8.2	11	—
9	8.6	19	—
10	9.0	14	—
11	10.0	20	35
12	10.4	24	—

ful. Inflation of the balloon with the tip just across the mitral valve resulted in catheterization of the pulmonary artery in only 40 per cent of our patients. The alternative method of forming a loop in the distal part of the catheter by manipulation of its tip against the lateral or inferior left ventricular wall is technically more difficult and requires considerable manipulation of the catheter. However, once the loop is formed, inflation of the balloon usually carries the catheter into the pulmonary artery (Figs. 1B and 1C). Although short runs of premature ventricular contractions occurred when the catheter tip was being manipulated against the left ventricular wall, only

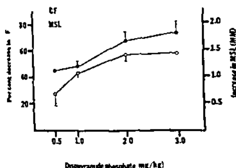


Fig 1 Relationship between the decrease in contractile force and the increase in muscle segment length after intravenous administration of disopyramide phosphate Each point represents mean ± S.E. from at least 6 dogs CF = contractile force MSL = muscle segment length

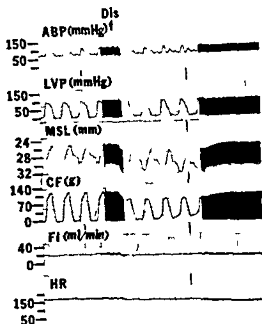


Fig 2 Typical responses to disopyramide phosphate 1 mg per kilogram of body weight intravenously Paper speed 0 25 mm. per second for slow tracings and 50 mm per second for fast tracing Dis = disopyramide phosphate ABP = aortic blood pressure LVP = left ventricular pressure Fl = coronary blood flow HR = heart rate Other abbreviations as in Fig 1

dicular to the anterior interventricular sulcus This gauge was similar to that used by Newman and Walton[3] and accurately reflected small changes in the length of a 24 mm (± 0 5 mm) muscle segment In some dogs the mural force also was measured by a Hefner type strain gauge arch which responded to the force developed within the wall of the left ventricle[4] thus reflecting alterations in intraventricular pressure or size

Polyethylene catheters (PE 240) were placed in the femoral vein and artery for injections of drugs and measurements of arterial blood pressure with a Statham P23AC transducer The left ventricular pressure was measured by a Statham P23AA transducer connected to a short stiff segment of nylon catheter passed into the ventricular chamber through the apical dimple Coronary blood flow was recorded from the anterior descending coronary artery by a precalibrated Medicon sine wave electromagnetic flowmeter Heart rate was monitored by a tachometer All recordings were made with a Sanborn model 150 Polyviso recorder

In order to relate mural force changes to load changes produced in the ventricle by SC 13957 and quinidine a correlation was obtained between the left ventricular variables mural force and the product of intraventricular pressure multiplied by an index of internal radius squared PR_i^2 PR_i^2 an indication of myocardial wall tension (distending force) was measured during the period of isometric systolic contraction phase at 10 millisecond intervals for three consecutive beats P represents the ventricular systolic pressure and R_i^2 the square of the internal radius of the ventricle Estimates of the internal radius were obtained from high speed muscle segment length recordings according to the method of Newman and Walton[3]

Beta adrenergic blocking activity of SC 13957 was tested in three dogs by observing the response of the contractile force and aortic blood pressure to isoproterenol tyramine or norepinephrine before and after intravenous administration of SC 13957 in doses of 1 to 10 mg per kilogram of body weight

Student s t test for paired data was used to test statistical significance[5] Values with $P < 0.05$ were considered significantly different from controls

Results

The effects of SC 13957 on the parameters studied are summarized in Table I and

Experimental and laboratory reports

Cardiovascular effects of a newer antiarrhythmic agent, disopyramide phosphate

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Disopyramide (r diisopropylamino al pha phenyl alpha (2 pyridyl) butyramide) is an effective antiarrhythmic agent in man and in experimental animals[1,2] Its antiarrhythmic properties are at least equal to those of quinidine, and it is in some instances more potent[1,2] Use of this drug clinically would depend primarily on the ratio of toxic to therapeutic effects Diso pyramide has a low degree of toxicity[1] but like quinidine it is a myocardial depressant in isolated heart studies In order to ex plore further the pharmacologic effects of this agent a study was made in the anes thetized dog for its action on myocardial contractile force coronary blood flow, muscle segment length, aortic and left ventricular pressures and Lead II of the electrocardiogram (ECG) Its effectiveness as a beta adrenergic blocking agent was also examined Since the phosphate salt of disopyramide had been approved by the Food and Drug Administration for clinical trial,† disopyramide phosphate (SC 13957) was chosen in this study Quinidine sulfate was used for comparison

Methods

Healthy adult mongrel dogs (males or females in anestrus) weighing 10 to 25 kilograms were anesthetized by intravenous administration of 30 mg per kilogram of body weight sodium pentobarbital Light surgical levels of anesthesia were maintained by additional intraperitoneal injections of sodium pentobarbital in small doses Artificial respiration with room air was instituted with a Harvard positive pressure respirator following tracheal intubation A left thoracotomy was performed in the fifth intercostal space and the pericardium was incised and sutured to the chest wall to support the heart In all animals myocardial contractile force, arterial blood pressure left ventricular pressure coronary blood flow muscle segment length and heart rate were monitored Electrocardiogram (Lead II) was recorded at a speed of 50 mm per second and alterations were observed at drug concentrations varying from 1 to 10 mg per kilogram of body weight

Contractile force was measured by a precalibrated Walton Brodie strain gauge arch with adjustable foot sutured directly onto the left ventricle within the area of distribution of the anterior descending coronary artery The muscle segment was stretched 40 per cent A precalibrated sensitive isotonic strain gauge arch was sutured onto the left ventricle parallel to the Walton Brodie gauge and nearly perpen

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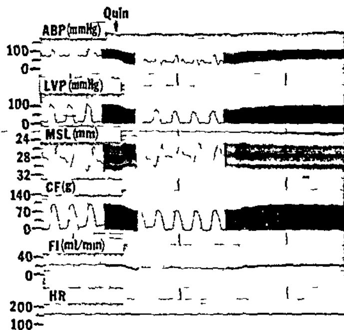


Fig 3 Typical responses to quinidine sulfate 5 mg per kilogram of body weight intravenously *Quin* = quinidine Other abbreviations and paper speed same as in Fig 2

duration) was lower with SC 13957 The effects of the two drugs on A V conduction were similar

Unlike SC 13957 quinidine caused a transient decrease in muscle segment length (Fig 3) This effect could have been due to the significant lowering of peripheral vascular resistance or to decreased filling pressure To test this hypothesis aortic pressure was maintained mechanically by placing partial constriction around the aorta during the administration of quinidine In this experiment quinidine increased the heart size by increasing muscle segment length and hence resembled SC 13957 qualitatively (Fig 5) Similar responses were obtained in three other dogs tested

The mural force showed a high degree of correlation with the load of the ventricle PR[2] with linear correlation coefficient r ≥ 0 99 Following administration of disopyramide phosphate or quinidine this linear correlation between mural force and PR[2] was not altered Data obtained in one of the three such experiments is illustrated in Fig 6

In doses of 1 to 10 mg per kilogram of body weight SC 13957 did not block the response of the myocardial contractile force and aortic blood pressure to 60 μg per kilogram of body weight of tyramine or 1 μg per kilogram of body weight norepinephrine or 1 μg per kilogram of body weight isoproterenol (Fig 7)

Discussion

Compared to quinidine the alterations in contractile force and muscle segment length produced by SC 13957 were most discernible In the present in vivo study SC 13957 was more active in depressing the contractile force than quinidine and this effect was seen at a much lower dosage than that observed by Mokler and Van Arman[1] This difference in magnitude might be due to the species differences and/or the differences in the technique used Depression of the contractile force was discernible with 100 μg per kilogram of body weight of SC 13957 in two of the three dogs tested however the decrements at this dosage were transient control levels were restored within 2 to 3 minutes Higher doses of the drug exerted a correspondingly greater effect on the contractile force (Fig 1) and were longer lasting (20 to 30 minutes

Table I Effect of disopyramide phosphate on coronary flow, arterial, and left ventricular pressures

Intravenous dosage (mg/kg)	Coronary flow decrease (%)*	Left ventricular end diastolic pressure change (mm Hg)*	Arterial blood pressure change (mm Hg)*	
			Systolic	Diastolic
1 0	15 3 ± 2 2† (10)	+3 9 ± 1 13† (11)	−5 6 ± 1 96‡ (11)	+0 3 ± 1 44 (11)
2 0	29 1 ± 5 7† (11)	+4 6 ± 1 62‡ (8)	−11 5 ± 2 56† (8)	−5 8 ± 1 50† (9)
3 0	37 2 ± 9 0‡ (4)	+5 5 ± 0 96† (6)	−18 3 ± 2 65† (7)	−7 1 ± 3 78 (7)

*Mean ± S E. Number in parenthesis indicates the number of dogs.
†P < 0 01
‡P < 0 05

Table II Effect of quinidine sulfate on cardiovascular dynamics

Dog no	Intravenous dosage (mg/kg)	Contractile force decrease (%)	Maximum MSL decrease† (%)	LVEDP change† (mm Hg)	Arterial blood pressure change (mm Hg)		Coronary blood flow decrease (%)
					Systolic	Diastolic	
1	1 0	0	0	0	0	0	0
	2 0	0	0	0	0	0	0
	5 0	0*	1 5	−5	−23	−20	10 0
	10 0	12 5	1 3	0	−40	−35	28 5
	15 0	33 3	1 5	0	−70	−50	42 9
2	1 0	0	0	0	0	0	0
	2 0	14 3	1 5	0	−55	−40	36 4
	5 0	17 4	0 5	+5	−25	−33	44 4
	10 0	66 7	1 8	−5	−55	−40	42 9
3	2 0	0	0	0	0	0	0
	5 0	28 5	2 5	−5	−25	−30	16 7
4	2 0	0	0	0	0	0	0
	5 0	36 4	1 5	0	−15	−30	10 0

*No change in contractile force was present over the period in which depression was usually observed but there was an initial brief increase in contractile force
†Abbreviations MSL = muscle segment length LVEDP = left ventricular end diastolic pressure

Fig 1 and the typical responses are illustrated in Fig 2 For comparison, the effects of quinidine sulfate are summarized in Table II and Fig 3

SC 13957 in doses as low as 1 mg per kilogram of body weight significantly depressed the myocardial contractile force systolic aortic pressure, and coronary blood flow, and increased muscle segment length These effects were dose related (Table I and Fig 1) The chronotropic responses to SC 13957 and quinidine were similar and were slightly but not significantly reduced from control values

Compared to quinidine, effects of SC 13957 on the ECG (Lead II) were similar except for minor differences at drug concentrations varying from 1 to 10 mg per kilogram of body weight (Fig 4) SC 13957 has slightly less pronounced effects on widening of the QRS complex indicating that quinidine slowed the ventricular conduction rate to a greater extent than SC 13957 however atrial nduction (P



Table I. Effect of disopyramide phosphate on coronary flow, arterial, and left ventricular pressures

Intravenous dosage (mg/kg)	Coronary flow decrease (%)*	Left ventricular end diastolic pressure change (mm Hg)*	Arterial blood pressure change (mm Hg)*	
			Systolic	Diastolic
1.0	15.3 ± 2.2† (10)	+3.9 ± 1.13† (11)	−5.6 ± 1.96‡ (11)	+0.3 ± 1.44 (11)
2.0	29.1 ± 5.7† (11)	+4.6 ± 1.62‡ (8)	−11.5 ± 2.56† (8)	−5.8 ± 1.50† (8)
3.0	37.2 ± 9.0‡ (4)	+5.5 ± 0.96† (6)	−18.3 ± 2.65† (7)	−7.1 ± 3.78 (7)

*Mean ± S.E. Number in parenthesis indicates the number of dogs.
†$P < 0.01$
‡$P < 0.05$

Table II. Effect of quinidine sulfate on cardiovascular dynamics

Dog no.	Intravenous dosage (mg/kg)	Contractile force decrease (%)	Maximum MSL decrease† (%)	LVEDP change† (mm Hg)	Arterial blood pressure change (mm Hg)		Coronary blood flow decrease (%)
					Systolic	Diastolic	
1	1.0	0	0	0	0	0	0
	2.0	0	0	0	0	0	0
	5.0	0*	1.5	−5	−23	−20	10.0
	10.0	12.5	1.3	0	−40	−35	28.5
	15.0	33.3	1.5	0	−70	−50	42.9
2	1.0	0	0	0	0	0	0
	2.0	14.3	1.5	0	−55	−40	36.4
	5.0	17.4	0.5	+5	−25	−33	44.4
	10.0	66.7	1.8	−5	−55	−40	42.9
3	2.0	0	0	0	0	0	0
	5.0	28.5	2.5	−5	−25	−30	16.7
4	2.0	0	0	0	0	0	0
	5.0	36.4	1.5	0	−15	−30	10.0

*No change in contractile force was present over the period in which depression was usually observed, but there was an initial brief increase in contractile force.
†Abbreviations: MSL = muscle segment length; LVEDP = left ventricular end diastolic pressure.

Fig. 1, and the typical responses are illustrated in Fig. 2. For comparison, the effects of quinidine sulfate are summarized in Table II and Fig. 3.

SC 13957 in doses as low as 1 mg. per kilogram of body weight significantly depressed the myocardial contractile force, systolic aortic pressure, and coronary blood flow, and increased muscle segment length. These effects were dose related (Table I and Fig. 1). The chronotropic responses to SC 13957 and quinidine were similar, and were slightly but not significantly reduced from control values.

Compared to quinidine, effects of SC 13957 on the ECG (Lead II) were similar, except for minor differences at drug concentrations varying from 1 to 10 mg. per kilogram of body weight (Fig. 4). SC 13957 has slightly less pronounced effects on widening of the QRS complex, indicating that quinidine slowed the ventricular conduction rate to a greater extent than SC 13957; however, atrial conduction (P

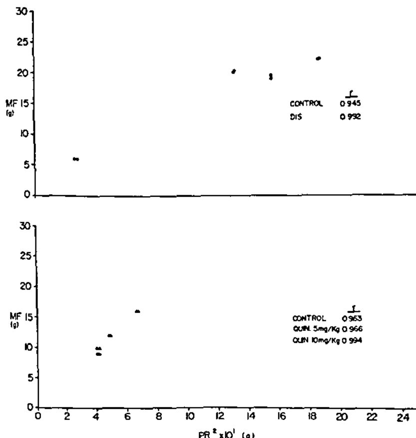


Fig 6 Linear correlation between mural force measured by a Hefner type strain gauge and PR, (calculated distending force) before and after disopyramide phosphate 1 mg per kilogram of body weight and quinidine sulfate 5 and 10 mg per kilogram of body weight intravenous administration All measurements were made during the period of isometric systolic contraction phase at 10 millisecond intervals for three consecutive beats P represents the ventricular systolic pressure and R^2 the square of internal radius of the ventricle r = linear correlation coefficient Similar data were obtained in three other separate experiments

activity and in similar doses possessed more cardiac depressant properties than quinidine However for the same degree of cardiac depression (contractile force) SC 13957 exhibited less of electrocardiographic abnormalities particularly on the ventricular and atrial conduction system and hence could be used as a replacement therapy for quinidine The use of disopyramide in patients requiring higher dosages of SC-13957 should be guarded with extreme caution because it induces a high degree of cardiac depression and increases the heart size.

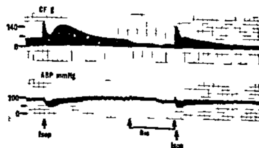


Fig 7 A typical recording for the response of aortic blood pressure and contractile force to isoproterenol 1 µg per kilogram of body weight before and after disopyramide phosphate 5 mg per kilogram of body weight. Similar response was obtained with tyramine 60 µg per kilogram of body weight or norepinephrine 1 µg per kilogram of body weight. *Isop* = isoproterenol Other abbreviations and paper speed are the same as in Fig 2

Summary

The effect on myocardial contractility of a new antiarrhythmic drug disopyramide phosphate was investigated and compared

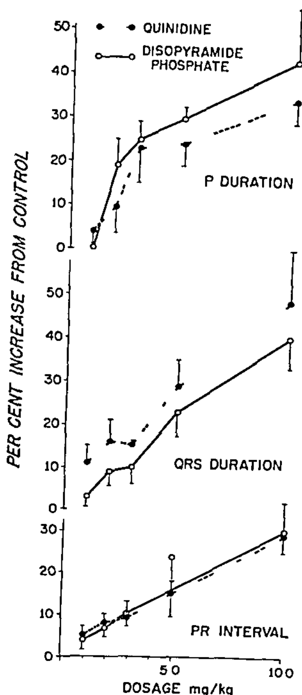


Fig 4 Effect of drugs on Lead II of the electrocardiogram

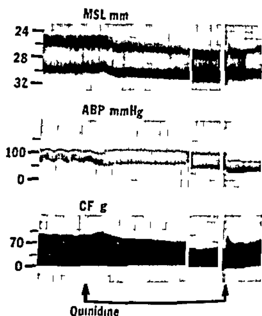


Fig 5 An experiment to show the response of the heart size and contractile force to quinidine sulfate 5 mg per kilogram of body weight intravenously with the aortic pressure held constant by a mechanical constriction around the descending aorta Abbreviations and paper speed are the same as in Fig ?

with 10 mg per kilogram of body weight) This effect of SC 13957 was not caused by beta adrenergic blockade because the drug did not block the response of the contractile force to isoproterenol (Fig 7)

The chronotropic and inotropic state of the heart are determinants of cardiac oxygen consumption [6,7] In the present study, SC 13957 reduced the contractile force and coronary blood flow while the heart rate remained unaltered The finding of a reduced contractile force and coronary blood flow prompted an inquiry in the direction of myocardial oxygen consumption, the latter was found to be reduced significantly in another series of experiments (unpublished observation)

Drugs which depress myocardial contractility also increase the heart size [8,9] Similar observations were found for SC 13957 in the present study (Fig 2) The decrease in heart size observed after quinidine, even though of little magnitude was consistently present in all experiments and probably was due to certain compensatory mechanisms such as after load of the heart or decreased filling pressure secondary to a fall in aortic pressure When the latter was held constant by mechanical constriction of the aorta the heart size increased after quinidine administration (Fig 5)

When the calculated ventricular wall tension (myocardial distending force), PR_i^2, was correlated with the mural force, a good linear correlation coefficient was obtained ($r \geq 0.90$ Fig 6) Neither SC 13957 nor quinidine altered this correlation

In conclusion SC 13957 apparently was devoid of beta adrenergic receptor blocking

The intimal proliferation in aortic-coronary saphenous vein grafts

Light and electron microscopic studies

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The wide acceptance of saphenous vein grafts in the surgical treatment of occlusive coronary artery disease[1] makes the changes that occur in the grafts and their ultimate fate of considerable importance Reports of series of autopsy cases indicate that grafts in place for one month or longer show fibrous intimal thickening or intimal fibrosis with associated proliferation of smooth muscle cells and medial fibrosis[2] The pathologic changes in 16 saphenous vein grafts were further studied including the ultrastructure of one which was excised after having been in place for 21 months

Material and methods

From February 25 1969 through December 31 1971 410 aortic-coronary saphenous vein graft procedures were performed at the Hospital of the Good Samaritan Medical Center Of these 13 patients came to autopsy from two days to 29 months after the surgical procedure and three more saphenous vein grafts were excised surgically after having been in place from six to 23 months The reports and slides from all cases were reviewed In all instances the vein grafts had been grossly completely examined most by multiple cross sections Some had also been opened in part longitudinally The degree of stenosis areas of occlusion and the patency of anastomoses to the aorta and the distal segments of the coronary arteries had been noted Representative sections from all cases were studied and were compared with the sections from unused segments of the saphenous vein excised at the time of the bypass procedure

One of the segments of vein (B 5282 71) when excised and replaced surgically because of an angiographically demonstrated occlusion was dissected in the operating room Representative portions of the occlusive luminal tissue were prefixed for two hours in 2 0 per cent cacodylate buffered glutaraldehyde and postfixed for one hour in 1 0 per cent cacodylate buffered osmic acid The pieces of tissue were then dehydrated in a graded series of acetone and

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with that of quinidine using a Walton Brodie strain gauge arch Quinidine and disopyramide phosphate were compared at the same dosage ranging from 1 to 10 mg per kilogram of body weight At 1 mg per kilogram of body weight, the contractile force was unaffected by quinidine but was depressed 42 per cent by disopyramide phosphate At higher doses (5 to 10 mg per kilogram of body weight) the contractile force was depressed 50 to 100 per cent more by disopyramide phosphate than by quinidine End diastolic muscle segment length increased 5 per cent with disopyramide phosphate at 1 mg per kilogram of body weight whereas no change was observed with quinidine at this dosage Both drugs widened QRS and P duration and prolonged PR interval to the same degree Disopyramide appears to have no beta adrenergic blocking activity since it did not alter the contractile force or arterial blood pressure responses to isoproterenol norepinephrine or tyramine Coronary blood flow was decreased by both drugs The cardiac depressant effect of disopyramide phosphate would appear to limit its usefulness but for the same degree of cardiac depression, disopyramide phosphate exhibited fewer ECG abnormalities and hence could be used as a replacement therapy for quinidine

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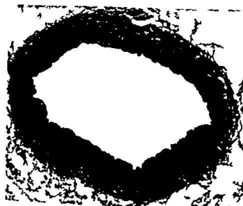


Fig 1 Normal saphenous vein (unused segment) The internal elastic layer is distinct and the intima s very thin (Verhoeff-elastic Original magnification X20)



Fig 2 Proliferating predominantly fibrous intimal plaque two months after grafting (Hematoxylin and eosin. Original magnification X50)



Fig 3 Circumferential intimal fibrosis with resulting stenosis seven months after grafting (Hematoxylin and eosin Original magnification X20)



Fig 4 Groups of lipid filled macrophages in fibrosed intima of vein 29 month after grafting (Hematoxylin and eosin Original magnification X50)

pre-existing mural thrombi One of the veins (Case 16) which had been in place for 29 months also contains collections of lipid filled macrophages within the thickened fibrotic intima resembling early arterial atheromatous plaques (Fig 4) The intima in this case is less cellular and more collagenous than in the cases of shorter duration

Five of the veins which had been in place from 5 to 23 months were occluded by fibrous tissue The occlusion generally extended the full length of the grafted segment Portions of the occlusive fibrous tissue resemble more cellular intima in the only partially occluded or stenosed segments but in other areas the entire lumen is filled by relatively acellular partially hyalinized fibrous tissue containing a few capillary vascular spaces Larger channels of recanalization are not seen

Electron microscopic studies of the tissue occluding the lumen within the internal elastic membrane in Case 14 show several characteristic cell types These include cells rich in rough surfaced endoplasmic reticulum that appear to be active fibroblasts (Fig 5) More frequently the cells exhibit a shallow layer of cytoplasm with many free ribosomes but little rough surfaced membranes These cells are considered to be quiescent fibrocytes (Fig 6) Macrophages containing many dense inclusion bodies are also present as are small

Table I. Pathologic changes in saphenous vein grafts

Case	Number	Sex	Age (yr.)	Graft in place	Changes in grafted saphenous vein
1	(BA 201 71)	M	49	2 days	No significant change
2	(BA 74 71)	M	62	8 days	Thrombosis, partially occlusive
3	(BA 45 71)	M	63	12 days	Minimal intimal fibrosis
4	(BA 138 70)	M	61	15 days	Edema—no significant change
5	(BA 203 71)	M	53	21 days	Slight focal intimal fibrous thickening
6	(BA 54 71)	M	40	28 days	Slight intimal fibrosis and occlusive thrombosis
7	(BA 81 69)	M	50	30 days	Thrombosis, organizing, occlusive
8	(BA 254 70)	M	61	2 months	Intimal fibrous plaques and slight stenosis
9	(BA 176 71)	M	62	5 months	Intimal fibrosis, occlusive
10	(B 4357 71)	M	46	6 months	Intimal fibrosis, occlusive
11	(BA 210 71)	M	62	7 months	Intimal fibrosis, stenosing
12	(BA 212 71)	M	69	8 months	Intimal fibrosis, occlusive
13	(BA 171 71)	M	53	17 months	Intimal fibrosis, severe stenosing
14	(B 5282 71)	M	56	21 months	Intimal fibrosis, occlusive
15	(B 3866 71)	M	43	23 months	Intimal fibrosis, occlusive
16	(BA 120 71)	M	51	29 months	Intimal fibrosis, severely stenosing

embedded in a polyester resin. Two micron sections stained with toluidine blue were examined in a light microscope and representative intimal areas were identified. Thin sections from these areas were then stained with uranyl acetate and lead citrate and examined in a Hitachi 8S electron microscope.

Results

The principal pathologic changes are summarized in Table I. All patients in the study group were men and ranged in age from 40 to 69 years. The saphenous vein grafts had been in place from two days to 29 months. In the seven cases in which the graft had been inserted for 30 days or less there were no or only minimal intimal changes characterized by slight edema or minimal fibrosis. In three cases the graft was found to be occluded by thrombi eight, 28, and 30 days after surgery. In the remaining nine cases in which the graft had been in place from 2 to 29 months, there were moderate to severe intimal fibrotic changes. These intimal changes are particularly striking since in corresponding nongrafted segments of saphenous veins the intima consists of a very thin layer inside the internal elastic membrane (Fig. 1). The intimal fibrosis becomes increasingly more prominent with extended periods of emplacement. In early periods as in Case 8 after two months it may be irregular in thickness and plaque-like (Fig. 2). The plaques in this case contain histiocytes as well as fibroblasts. Special stains demonstrate the presence of few small lipid droplets. Hemosiderin or distinct endothelial proliferation are not noted. In three other cases, 7 months, 17 months, and 29 months after grafting, the intimal fibrosis was circumferential and stenosing (Fig. 3). Cardiac catheterization studies performed one to two months prior to the death of these patients had demonstrated patent graft. The gross examination of the cross-sectioned veins showed them to be of slightly decreased external diameter and to have a thickened and indurated wall with an internal luminal diameter from 1 to 3 mm. This compares with an average of 3 to mm. of the usual resected segment of saphenous vein when used for the bypass graft. Microscopically, the lumen within the usually intact internal elastic membrane is lined by a thick layer of predominantly fibrous tissue and is stenosed (Fig. 3). In few of the multiple sections small mural thrombi are found attached to the inner lining but the histologic appearance as well as the circumferential, fairly regular distribution of the fibrous layer extending from the aortic ostium to the site of anastomosis with the distal branch of the coronary artery, do not suggest an origin from th



Fig 8 Smooth muscle cell within occlusive intimal tissue Note the strand like cytoplasmic dense bodies and flask like invaginations of the cell membrane (Original magnification X11 000)

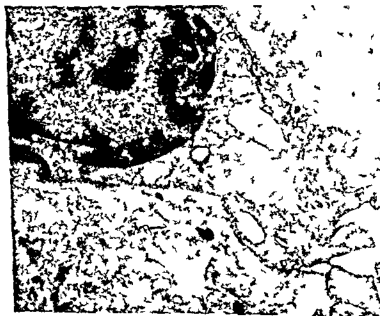


Fig 9 Portion of smooth muscle cell Thin filaments associated with dense bodies and many small invaginations of the plasma membrane are characteristic The cytoplasm also contains a lipid inclusion. (Original magnification X24 000)



Fig 5 Fibroblast rich in rough surfaced endoplasmic reticulum The membrane bounded cisternae are distended with flocculent material (Original magnification ×18 000)



Fig 6 Quiescent fibrocyte exhibiting a shallow layer of cytoplasm containing little rough surfaced endoplasmic reticulum and many free ribosomes (Original magnification ×11 000)

capillary blood vessels lined by endothelial cells (Fig 7)

One of the cell types shows features characteristic of smooth muscle cells[4,6] These cells are elongated or spindle shaped with elongate nuclei oriented in the long axis of the cells Within the cytoplasm thin filaments parallel to the long axis of the



Fig 7 Newly formed capillary within intimal proliferating tissue of grafted vein (Original magnification ×8 000)

cells and strand like cytoplasmic densities characteristic of "dense bodies" are present (Figs 8 and 9) Other specialized structural features that have been associated with smooth muscle cells are flask like invaginations of the cell membrane and dense cytoplasmic material lying adjacent to the plasma membrane Some of the smooth muscle cells contain characteristic lipid inclusions (Fig 9) resembling the inclusions seen in smooth muscle cells of early atherosclerotic lesions[7]

Comment

This study of a relatively large number of cases confirms earlier reports of significant intimal changes in the saphenous veins used for aortic coronary bypass grafts after they have been in place for approximately one month[2,3] While Vlodaver and Edwards[2] stress the fibrous nature of the intimal proliferative tissue Marti Bonchardy and Cox[3] also describe transient muscular hypertrophy and eventual fibrosis of the media and the presence of smooth muscle cells in the predominantly fibrous intimal layer Our findings clearly demonstrate that the process is predominantly an intimal one but some fibrosis is also evident in the media and the over all diameter of the vessels is decreased probably partially due to this medial fibrosis Intimal fibrosis, first in an uneven distribution but eventually circumferential, is the most uniform change and is present in all veins after approximately one month It probably represents a reparative phenomenon responding to unusual hemodynamic stress[3] The

atheromatous changes within the thickened fibrosed intima The ultrastructure of one of the occlusive fibrotic lesions demonstrated the presence of histiocytes newly formed capillary blood vessels fibroblasts and characteristic smooth muscle cells some of which contained lipid vacuoles in the cytoplasm

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changes are not unlike those observed in the veins affected by congenital or traumatic arterial venous shunts as a result of increased pressure and blood flow.[8] In three of the cases studied during the first month after surgery, the graft lumen was occluded by thrombi. In the four cases with stenosing intimal fibrosis there was no histologic evidence of preceding organizing thrombosis, but it must be recognized that some arterial fibrous plaques in the early stages of arteriosclerosis are thought to represent arterial mural thrombi[5] and that the pathogenesis of such fibrous plaques in arteries or veins can not be satisfactorily resolved on a morphologic basis. The circumferential nature and uniform distribution from the site of the aortic ostium to the distal anastomosis indicate that this is in all probability a reactive or reparative process rather than organizing thrombosis. It is more difficult to determine whether the occlusive luminal fibrosis observed in five other cases also represents the final stage of intimal reactive fibrosis or an old organized thrombus. The bland nature of the fibrous tissue, absence of recanalization, uniform distribution through much or all of the length of the graft, and similarity of portions of these tissues to the circumferential intimal fibrosis make it appear likely that this process was at least initially circumferential fibrosis, perhaps with terminal thrombosis and organization of a remaining narrowed lumen.

It is of great practical importance whether the described intimal fibrosis will progress in many cases until the vessels have become occluded or whether it is self limited. The 16 cases reported in this study represent a relatively small percentage of the 410 patients operated upon and are those with the least favorable results. Nevertheless, the presence of considerable fibrosis in all vessels that were examined after being in place for longer than one month indicates that such changes probably do exist in most or all grafted veins. Only long range angiographic and pathologic follow up studies will demonstrate how extensive these changes are in the majority of patients and how many vessels eventually will become obliterated.

The ultrastructure of the intimal proliferating tissue and the presence of smooth muscle cells are of particular interest. The intima of normal veins is only feebly developed and contains an inconspicuous connective tissue layer with few cells and thin elastic fibers[9] (Fig. 1). Smooth muscle cells are not described in the intima of normal veins but are present when the intima of arteries becomes diffusely thickened with increasing age.[10] The demonstrated presence of smooth muscle cells in the fibrosed intima of "arterialized" grafted veins appears to correspond to these long recognized arterial changes.

In addition to the presence of smooth muscle cells in aging thickened intima, scattered smooth muscle cells are found in fatty streaks, the earliest atherosclerotic changes of arteries.[11] Geer, McGill, and Strong[7] demonstrated the presence of lipid in smooth muscle cells of fatty streaks and considered these changes to represent lipid synthesis in situ. Modified smooth muscle cells have also been demonstrated in intimal lesions of the rat aorta, but some questions have been raised as to the identity of these intimal cells with smooth muscle cells elsewhere in the body because of the relative nonspecificity of various morphologic criteria.[12] The morphologic features of the elongated cells demonstrated in the intimal tissue in our study closely correspond to those considered characteristic of smooth muscle cells[6] and we believe these cells can be accepted as being of this origin. The presence of lipid vacuoles in some of the smooth muscle cells but particularly the presence of clusters of characteristic lipid filled macrophages within the thickened fibrosed intima in one of the cases indicate the likelihood of the eventual development of atherosclerosis similar to changes observed in other veins exposed to increased pressures.[13]

Summary

The pathologic features of 16 aortic coronary saphenous vein grafts which had been in place from 2 days to 29 months were reviewed. Thirteen cases came to autopsy and three vessels were surgically re excised. The nine cases which had been in place for two months or longer showed considerable intimal fibrosis. Four were stenosed and five were occluded. One of the vessels, 29 months after grafting, showed

Table I *Clinical data for 14 patients*

Patient	Sex	Age	Type of heart disease	Reason for catheterization	Drugs administered
P L.	M	64	ASHD	CHF VPC s	
L E.	M	45	ASHD aortic stenosi	Chest pain	None
D G.	M	67	Cardiomyopathy	VPC s mild CHF	None
L. R.	M	66	ASHD	VPC s	Pronestyl 2 Gm /day none for 2 days
G D	M	65	Pulmonary disease	Syncope RBBB 1 AVB	None
D G	M	52	None	Palpitations WPW	None
A M	M	57	ASHD	Angina	None
M H	M	71	Cardiomyopathy (?)	VPC s	None
L M	F	59	ASHD	Angina mild CHF	digoxin 0 25 mg /day Lasix 40 mg /day none for 1 day
E. D	M	60	ASHD	Angina	None
A. U	M	60	ASHD	Angina	None
W K.	M	44	ASHD	Short PR palpitation angina	Inderal 80 mg /day none for 2 days
D S	M	46	ASHD	Angina	None
D T	M	58	Pulmonary disease	VPC s APC s	None

Abbreviations ASHD = [illegible] CHF = co[illegible] VPC = [illegible] premature contraction RBBB = right bundle branch block AVB = [illegible] block WPW = Wolff P[illegible] White syndrome PR = PR interval APC s = atrial premature contractions.

every eighth paced atrial beat until refractory periods were determined

After control RP s were determined a 1 mg per kilogram of body weight bolus of lidocaine was given intravenously An intravenous drip was then started at 1 mg per minute and continued during the study period Five minutes were allowed for equilibration and then refractory studies were repeated Time lines were recorded at 10 and at 100 msec Data were stored on magnetic tape† and were later recorded at a paper speed of 150 mm per second ‡ The statistical data were analyzed using the Student s t test for paired data

Definition of terms The A H (atrium to His) interval as measured in the His bundle electrogram recording was taken as a measure of A V nodal conduction time (normal 60 to 140 msec)

The H V (His to ventricle) interval was taken as a measure of His Purkinje conduction time (normal 35 to 55 msec)

The effective refractory period (ERP) of the atrium is defined as the longest S_1-S_2 that does not result in atrial depolarization

The ERP of the AVN is the longest A_1 A_2 interval at which A_2 depolarizes the atrium but does not propagate to the HPS

The ERP of the HPS is the longest H_1 H interval at which H fails to depolarize the ventricles

The relative refractory period (RRP) of the HPS is the longest H_1 H_2 interval at which H_2 conducts to the ventricles with a longer H V interval than that of the basic drive beat or with a QRS or aberrant configuration This definition presupposes that the HPS functions as a single unit Although it is recognized that the HPS is a trifascicular system in the absence of multiple recording sites along individual fascicles it is impossible to precisely measure the ERP versus the RRP of any given fascicle Thus for the purposes of this study it was elected to consider the HPS as a single functioning unit and the RRP as so defined

Results

The results are summarized in Table II

Atrium The ERP of the atrium was not significantly changed by lidocaine In eight

†T[illegible]tronix P[illegible]rtland, Ore
‡North American Philips Co [illegible] Co[illegible]
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Effects of lidocaine on refractory periods in man

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Lidocaine is probably the most widely used antiarrhythmic agent in the treatment of ventricular arrhythmias due to a variety of causes[1-11] A few clinical reports have suggested that lidocaine may be effective in the treatment of some atrial arrhythmias[2,3,6,8,10,11] The electrophysiological effects of lidocaine on ventricular muscle and specialized conducting fibers using in vitro preparations have been investigated in detail[12-19] The effects of lidocaine on atrial muscle and the A V node have been less extensively studied[17] The present study was undertaken to determine the effects of lidocaine on the refractory periods of the atrium A V node and His Purkinje system in man by a systematic technique

Methods and materials

Fourteen patients were studied Seven had arrhythmias while the remainder were studied during the course of catheterization for other reasons after informed consent was obtained The pertinent clinical data of these patients is listed in Table I Right heart catheterization was performed in the nonsedated postabsorptive state Recordings from the His bundle were obtained according to methods previously described[3,4] In addition a quadrupolar electrode catheter was introduced via an antecubital vein and positioned fluoroscopically against the lateral wall of the right atrium The distal two electrodes were used to pace the right atrium while the proximal two recorded the high right atrial (HRA) bipolar electrogram Three or four surface electrocardiographic (ECG) leads (usually I II III and V_1) were simultaneously recorded In the majority of patients a bipolar electrode catheter was also positioned in the right ventricle Using a dual beam oscilloscope* and a programmed digital stimulator† which delivered impulses of 1 5 msec duration at twice diastolic threshold each patient was paced at a constant rate to avoid the effect of changing cycle length on refractoriness Refractory periods (RP s) of the atrium (A), A V node (AVN) and His Purkinje system (HPS) were determined by the extrastimulus method[2,20] Progressively premature atrial depolarizations were introduced after

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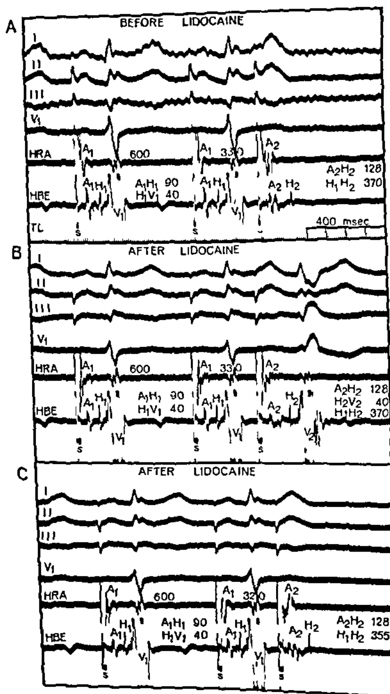


Fig. 1. *A* through *C*. Effect of lidocaine on the effective refractory period (ERP) of the His Purkinje system (HPS). Panel *A* demonstrates the H_1-H_2 interval at which block first developed within the HPS (370 msec.). After lidocaine (panels *B* and *C*) the H_1-H_2 interval at which block in the HPS occurred decreased from 370 to 355 msec.

Table II. Summary of results of lidocaine on refractory periods

Patient	Paced cycle length	ERP* of atrium before	ERP of atrium after	ERP of AVN before	ERP of AVN after	ERP of HPS before	ERP of HPS after	RRP of HPS before	RRP of HPS after
I I	600	300	250	300	320	—	—	—	—
I E	800	310	280	—	—	390	390	RBBB/LAD 450	RBBB/LAD 410
D G	800	290	310	410	380	—	—	RBBB/LAD 530	RBBB/LAD 475
I R	1000	425	350	450	320	—	—	—	—
G D	750	320	270	—	—	—	—	—	—
M H	600	280	280	370	330	—	—	—	—
L M	750	330	310	—	—	—	—	—	—
A U	900	330	320	370	<320	—	—	LBBB 480	LBBB 450
E D	900	300	310	—	—	450	425	RBBB/LAD 500	RBBB/LAD 475
M M	700	290	280	—	—	—	—	RBBB/LAD 380	Never aberrated
D G	700	315	270	370	370	—	—	—	—
W K	700	280	315	375	350	—	—	—	—
D S	600	290	305	—	—	370	355	RBBB/RAD 415	RBBB/RAD 385
D T	700	265	285	270	<285	370	355	RBBB/LAD 430	RBBB/RAD 390

Abbreviation: RBBB = right bundle branch block; LAD = left axis deviation; RAD = right axis deviation; LBBB = left bundle branch block; ERP = effective refractory period; AVN = atrioventricular node; HPS = His-Purkinje system; RRP = relative refractory period.

patients the ERP was shortened, in one there was no effect, and in five it increased. The mean change of −13 msec was not statistically significant ($p = 0.15$). However, three patients did show marked shortening of the ERP from 50 to 70 msec. The presence or absence of other drugs did not alter the effects of lidocaine on atrial refractoriness.

A-V node. The ERP of the AVN could be measured in only eight patients. In the remaining six the ERP of the atrium was reached before the ERP of the AVN could be determined. Lidocaine had variable effects on A-V nodal refractoriness. In four patients the ERP decreased, in three it increased, and in one there was no change. The mean effect of −24 msec was not statistically significant ($p = 0.30$). However, two patients did show marked shortening of the ERP of 50 and 130 msec.

His-Purkinje system ERP. Only four patients developed block within the HPS during control refractory period studies, and it was in these four that the effect of lidocaine on the ERP of the HPS could be determined. In three of the four patients lidocaine shortened the ERP by 15 to 25 msec, while in the fourth there was no change.

Fig. 1 shows the effect of lidocaine on the ERP of the HPS in one patient (D. S.). In the control state, panel *A*, the ERP of the HPS was determined to be 370 msec. After lidocaine, as shown in panels *B* and *C*, the ERP of the HPS was shortened to 355 msec.

His-Purkinje system RRP. During the premature atrial stimulation sequence, seven patients (I. E., A. U., M. M., W. K., D. S., E. D., and D. T.) manifested aberrant ventricular conduction in the form of RBBB with LAD (5), LBBB with normal QRS axis (1), and RBBB with RAD (1). In six out of seven patients lidocaine shortened the H_1-H interval at which aberration occurred and in one patient (M. M.) totally prevented aberration. Thus in all seven patients lidocaine shortened the RRP of the HPS. Fig. 2 is representative of this group.

Toxicity. There was one toxic reaction

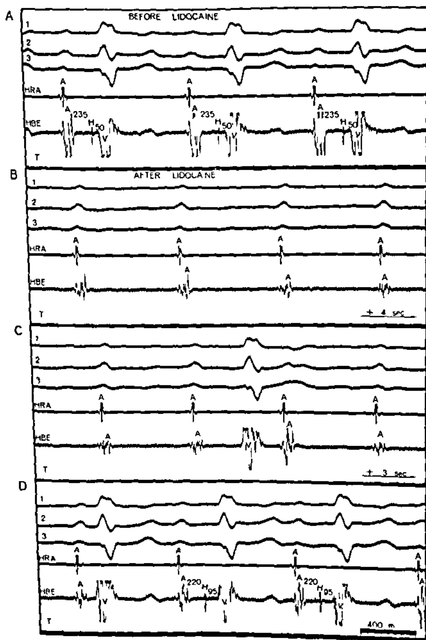


Fig 3 *A* through *D* This patient developed A V nodal block 15 minutes after lidocaine bolus and infusion was begun. Panel *A* shows control tracing with LBBB with an A H interval of 235 msec and an H V interval of 50 msec. Panels *B* through *D* show the evolution of lidocaine toxicity At first there is complete A V nodal block followed after several seconds by a ventricular escape beat. Eventually the patient resumed normal sinus rhythm (beats 2 and 3 in panel *D*) but the A H interval is now 220 msec. and the H V interval is now markedly prolonged at 95 msec. The arrows with +4 and +3 sec above them (panels *B* and *C*) indicated time elapsed before the subsequent tracing

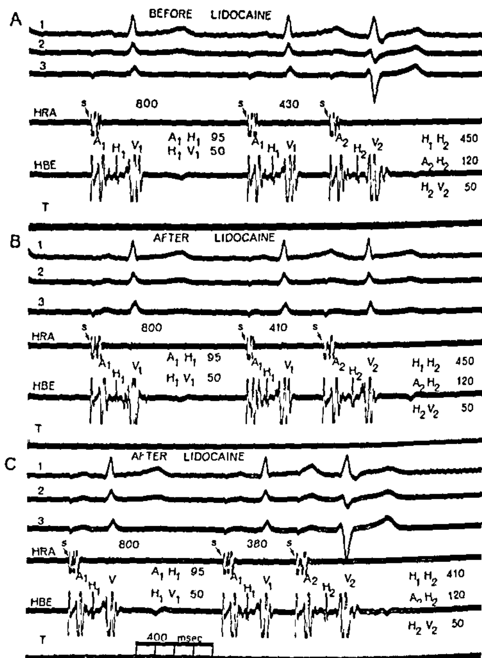


Fig 2 *A* through *C* Effect of lidocaine on the relative refractory period (RRP) of the HPS Before lidocaine (panel *A*) at a paced cycle length of 800 msec aberration with a RBBB and LAD occurred at an H_1 H_2 interval of 450 msec The lower two panels (*B* and *C*) show that after lidocaine no aberration occurred at an H_1-H_2 interval of 450 msec but at a shorter H_1 H_2 interval of 410 msec RBBB with LAD once again developed Lidocaine hortened the RRP by 40 msec

A fifteenth patient who was not included in the study developed a brief period of A V block and ventricular asystole fifteen minutes after an initial bolus of 100 mg lidocaine (Fig 3) Panel *A* shows the patient's ECG and HBE before lidocaine He had a LBBB with an H V interval of 50 msec Panels *B* through *D* show the evolution of lidocaine toxicity Initially there is complete A V nodal block and ventricular asystole A ventricular escape beat is seen after several seconds with subsequent reversion to normal sinus rhythm with LBBB (panel *D*) However, the H V interval is now 95 msec The bipolar electrode catheter which had been previously positioned in the right ventricle was used as a temporary standby pacemaker until the effects of lidocaine had dissipated

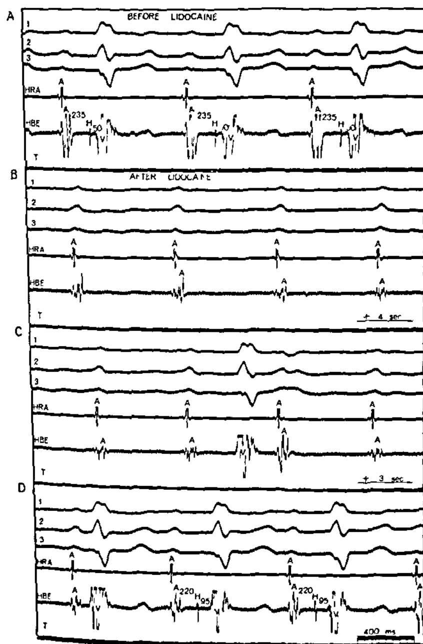


Fig. 3 A through D. This patient developed A V nodal block 15 minutes after lidocaine bolus and infusion was begun. Panel A shows control tracing with LBBB with an A H interval of 235 msec. and an H V interval of 50 msec. Panels B through D show the evolution of lidocaine toxicity. At first there is complete A V nodal block followed after several seconds by a ventricular escape beat. Eventually the patient resumed normal sinus rhythm (beats 2 and 3 in panel D) but the A H interval is now 220 msec. and the H V interval is now markedly prolonged at 95 msec. The arrows with +4 and +3 sec above them (panels B and C) indicated time elapsed before the subsequent tracing.

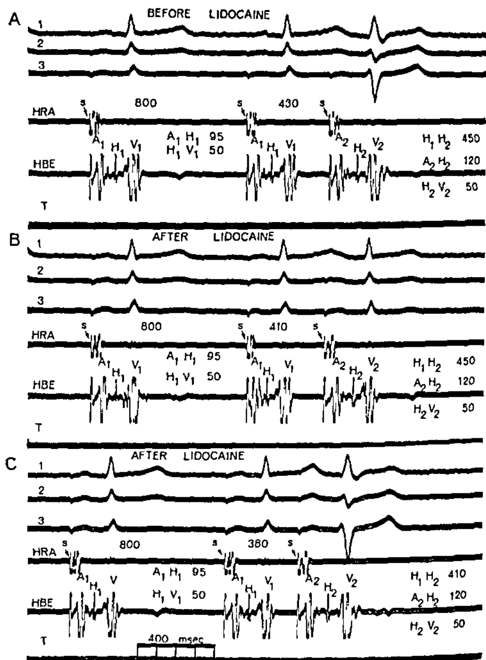


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Finally our study once again shows that therapeutic concentrations of lidocaine may have beneficial effects on the refractoriness of the HPS It suggests that lidocaine is a safer drug than Pronestyl or quinidine in the treatment of arrhythmias in the presence of varying degrees of heart block However despite its relative safety we observed the development of complete A V nodal block with ventricular asystole in one patient followed by persistent delay in HPS conduction upon return to normal sinus rhythm To our knowledge this reaction has not previously been reported Although moderate doses of lidocaine can abolish Phase 4 depolarization in Purkinje fibers[11, 12] (which is the probable mechanism of ventricular asystole in our case) the marked effects on the AVN and HPS were not seen in any other patient Since prolongation of A V nodal and HPS conduction is seen with toxic concentrations of lidocaine in vitro and although no blood levels were measured in our study it is most certain that this patient had toxic blood levels. In retrospect the patient had heart failure and probable cirrhosis both of which can and probably did lead to toxic blood levels of lidocaine[29, 30] due to delayed metabolism Therefore it is recommended that smaller than average doses of lidocaine be administered to patients with CHF or liver disease of any etiology

Summary

The effect of lidocaine on the refractory periods of the atrium A V node and His Purkinje system were studied using His bundle recordings and the extrastimulus method This method provides a safe and systematic approach to the evaluation of electrophysiological properties of drugs in man In usual therapeutic doses the present study demonstrated no consistent effect of lidocaine on the ERP of the atrium or the A V node However in these doses it shortened the ERP and the RRP of the His-Purkinje system These results explain the effectiveness of lidocaine in the management of ventricular arrhythmias and its inconsistency in the treatment of supraventricular rhythm disturbances The potential for lidocaine toxicity in the presence of heart failure and/or liver disease is noted

The authors wish to acknowledge the valuable assistance of Audrey Pedersen Mary Vecchione Michael Moretti Anne Mazzella and Kenneth Donohue

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*Table III. Effect of lidocaine on supraventricular arrhythmias**

Arrhythmia	*Episodes*	*Termination of suppression*	*Per cent*
APC†	38	23	60
JPC	4	3	75
PAT	16	6	38
SVT	13	3	23
Atrial flutter	11	2	18
Chronic atrial fibrillation	22	0	0
Acute atrial fibrillation	19	5	26
Total	123	42	34%

*See references 2, 4, 6, 8, 11.
†Abbreviations: APC = atrial premature contraction; JPC = junctional premature contraction; PAT = paroxysmal atrial tachycardia; SVT = supraventricular tachycardia.

Discussion

The effects of lidocaine on the refractory periods of various components of the A-V conducting system in man have not previously been reported. Rosen and co-workers,[9] using His bundle recordings, demonstrated that a single bolus of lidocaine had no significant effect on A-V nodal or His-Purkinje conduction time in man at various paced atrial rates. Sugimoto and associates[18] and Lieberman and colleagues[19] demonstrated variable prolongation of A-V nodal conduction time in the dog. This report extends the observations of these investigators.

Electrophysiological studies using microelectrode techniques have demonstrated that lidocaine produces a dose-related increase in the ERP of atrial tissue.[21, 22] However, at therapeutic or non-toxic concentrations (2.5 μg per milliliter), levels which are comparable to those achieved in the present study, lidocaine exerted no effect on atrial refractoriness. Thus our clinical observations are in agreement with these in vitro studies.

Similarly, our findings are in accord with the in vitro observations that lidocaine shortens the relative and effective refractory periods of Purkinje fibers at therapeutic concentrations.[12, 16] Thus in all areas of cardiac tissue studied, our observations in man mirrored in vitro microelectrode studies.

Clinical correlates. The usefulness of lidocaine in the management of ventricular arrhythmias is well documented.[1-11] The effects of lidocaine on refractoriness of the His-Purkinje system and its relevance to re-entrant ventricular arrhythmias has been discussed in detail.[12-16] However, its role in the treatment of supraventricular arrhythmias has not been evaluated. Table III lists the results of pooled data regarding the effects of lidocaine on supraventricular arrhythmias.[2, 4, 6, 8, 11] Lidocaine was able to control only about one third of the arrhythmias, with greatest success in atrial and junctional premature beats. This most likely represents the effect of lidocaine on Phase 4 depolarization of ectopic pacemakers. It is of little use in atrial flutter or fibrillation since it alters neither A-V nodal refractoriness nor conduction time and would, therefore, not be expected to slow the ventricular response in these arrhythmias. Since its effect on atrial refractoriness is also insignificant, it is not surprising that conversion of these atrial arrhythmias to normal sinus rhythm is unusual.

The reason for the failure of lidocaine to suppress re-entrant supraventricular arrhythmias has not been elucidated. An explanation for this stems from the recent work of Goldreyer and colleagues[27, 28] which showed that the site of re-entry in these arrhythmias was the A-V node. Since our study and that of Rosen and associates[9] showed no significant effect of lidocaine on A-V nodal refractoriness and conduction, it would not be expected to affect the re-entrant pathway and abolish these arrhythmias.

Finally our study once again shows that therapeutic concentrations of lidocaine may have beneficial effects on the refractoriness of the HPS It suggests that lidocaine is a safer drug than Pronestyl or quinidine in the treatment of arrhythmias in the presence of varying degrees of heart block However despite its relative safety we observed the development of complete A V nodal block with ventricular asystole in one patient followed by persistent delay in HPS conduction upon return to normal sinus rhythm To our knowledge this reaction has not previously been reported Although moderate doses of lidocaine can abolish Phase 4 depolarization in Purkinje fibers[11,12] (which is the probable mechanism of ventricular asystole in our case) the marked effects on the AVN and HPS were not seen in any other patient Since prolongation of A V nodal and HPS conduction is seen with toxic concentrations of lidocaine in vitro and although no blood levels were measured in our study it is most certain that this patient had toxic blood levels In retrospect the patient had heart failure and probable cirrhosis both of which can and probably did lead to toxic blood levels of lidocaine[29,30] due to delayed metabolism Therefore it is recommended that smaller than average doses of lidocaine be administered to patients with CHF or liver disease of any etiology

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Functional capacity of major anastomoses in chronically ischemic canine hearts

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In anatomic studies on pathological human hearts done by Schlesinger[1] and in Fulton's[2] studies with human and canine hearts the coronary collateral system has been shown to be a complex vascular network consisting of epicardial and mural components. Levy, Imperial, and Zieske[3] have shown with regional rubidium 86 myocardial uptake studies that the intramyocardial anastomoses are functionally significant in normal dogs. The interarterial epicardial collaterals in the chronically ischemic canine heart are generally regarded as the major routes for anastomotic flow;[4] however, their functional importance relative to the intramyocardial collateral system is unknown.

In this study the functional capacity of components of the collateral system was estimated by measuring changes in anastomotic flow following occlusion of the selected collateral vessels. Sequential occlusions of major groups of anastomoses were performed by either direct ligation of visible surface anastomotic communications or indirectly by occlusion of the normally perfused coronary arteries from which the anastomoses arise. Retrograde flow, an index of collateral flow, and actual collateral flow (krypton 85 myocardial clearance method) were determined prior to and following surgical interception of specific collateral channels.

Methods

The data to be reported were collected in experiments with ten normal dogs and six mongrel dogs subjected to chronic myocardial ischemia by placing Ameroid constrictors on their proximal circumflex arteries for periods of eight weeks or more prior to study (chronic preparations). Prior to terminal studies all animals (15 to 35 kilograms in weight) were anesthetized with 30 mg. per kilogram of body weight of intravenously administered pentobarbital, intubated, and ventilated with a Harvard pump respirator. The dogs were secured in the right lateral decubitus position and a left thoracotomy was performed. The pericardium was incised and sutured to the thoracic wall to minimize movement of the heart.

The circumflex artery just distal to the Ameroid constrictor was dissected, ligated proximally, and a large bore cannula was

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inserted just distal to the ligature and perfused from the left carotid artery through a series coupled polyethylene tubing, T tube, externally mounted A C electromagnetic flow probe as illustrated in Fig 1

The proximal anterior descending and right coronary arteries were dissected free and snares were positioned around them to induce transient intermittent occlusion of these arteries during the course of the experiment In one chronic preparation a snare was positioned around the primary septal artery

Following major surgical manipulations and prior to the insertion of all catheters, heparin (10 mg per kilogram of body weight) was given intravenously followed by repetitive doses of 2 mg per kilogram of body weight every thirty minutes

The electrocardiogram (ECG) and systemic pressure were monitored continuously throughout the experiment

All pressures and flows were obtained with Statham strain gauge transducers and Statham alternating current electromagnetic flow probes respectively, and were recorded with an Electronics for Medicine Recorder

1 *Retrograde flow measurement* The circumflex arterial cannula was opened to atmospheric pressures and retrograde flow collected in a volumetric flask for 20 to 30 seconds and concomitantly recorded with the circumflex cannula flow probe (Fig 1) In chronic preparations with large retrograde flows the pressure gradient across the circumflex cannula was estimated (e g predetermined circumflex cannula resistance × retrograde flow [flow probe]) and counterbalanced by adjusting the height of the retrograde flow outlet tubing to assure atmospheric to subatmospheric pressures at the arterial end of the cannula

2 *Collateral flow measurement* A Chicago Nuclear scintillation detector collimator was positioned over the left ventricle A two inch sodium iodide crystal was mounted 20 cm above the 10 cm diameter orifice of the collimator Saline solutions (0 2 to 0 5 c c) of krypton 85 yielding counts of 20,000 to 50 000 per minute were infused over periods of 5 to 10 seconds into the circumflex cannula system opened to systemic pressure Under these conditions the mean intraepicardial coronary pressure of the circumflex and adjacent coronary arteries are equal (phasic differentials are unavoidable) and the collateral flow is assumed equal to zero as is the delivery of krypton 85 to regions adjacent to the circumflex myocardial region

The time constant Kcx c c /min /100 Gm , was derived from the logarithmic clearance curves describing desaturation of the circumflex myocardial region with the circumflex cannula clamped and interpreted as the collateral flow per unit volume of this region To avoid induction of the ventricular fibrillation, the krypton 85 clearance phase was limited to 2 to 3 minutes in preparations (e g , normal dogs) subjected to severe myocardial ischemia The initial fast phase[5] of all clearance curves (5 to 10 second duration) was graphically eliminated and the stable linear phase was accepted as representative of mean clearance rates determined with infinitely long desaturation curves [6]

Duplicate determinations of (1) retrograde circumflex arterial flow and pressure and (2) krypton 85 circumflex myocardial clearance rates in selected studies were obtained prior to and following occlusion of specific collateral channels or the donor (normally perfused) coronary arteries from which the anastomoses arise

The anterior descending, right, and primary septal coronary arteries were selected for study as donor coronary vessels These vessels were subjected to transient occlusions by fastening snares at their proximal segments (Fig 1) The anteroapical epicardial anastomoses were ligated with 4 0 silk suture at their midpoints The epicardial anastomoses were identified with preligation coronary cineangiograms and their occlusions were verified with postligation coronary cineangiograms

At the conclusion of the experiment the anterior descending and right coronary arteries were ligated India ink was hand injected into the circumflex arterial cannula and the transit of ink through the arterial and venous networks and myocardium was observed

Results

In animals with chronically occluded circumflex arteries left coronary cineangi

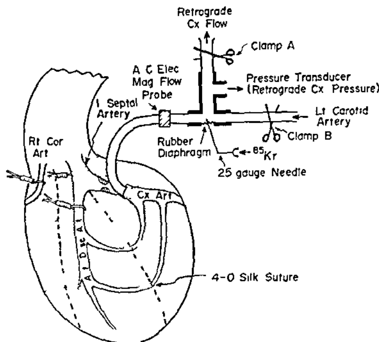


Fig 1 Diagrammati representation of typical dog heart as arranged for this study After the circumflex artery was d sected the cannula was inserted and perfused from the left carotid artery through tubing and externally connected to an electromagnetic flow probe *Ant Desc Art* = anterior descending artery *Cx Art* = circumflex artery ^{85}Kr = krypton 85

ography demonstrated 4 to 7 anastomotic communications between the anterior de scending and circumflex arteries along the anteroapical surface of the heart Right coronary cineangiography uncovered 1 to 2 large caliber collaterals supplying the recip ient distal circumflex artery Po t epicar dial collateral ligation left coronary cine angiography confirmed occlusion of the previously visualized anteroapical epicar dial collaterals

Following selective occlusion of the prox imal anterior descending artery the circum flex arterial retrograde flow was 12 per cent and retrograde circumflex pressure was 30 per cent of baseline (preocclusion) deter minations Following selective occlusion of the right coronary artery the retrograde cir cumflex arterial flow was 92 per cent (range 84 to 96 per cent) and retrograde circumflex pressure was 95 per cent (range 90 to 100 per cent) of baseline determinations Selec tive intermittent occlusions of the primary septal artery in one dog produced small (? to 5 per cent) but discrete reductions in retrograde flow as monitored with the cir cumflex cannula A C electromagnetic flow probe (Fig 1) concomitant occlusion of the proximal anterior descending artery and right coronary artery reduced retrograde flow to less than 1 per cent of baseline determinations (The systemic pressure was allowed to decrease spontaneously during these measurements)

The retrograde circumflex arterial flow and pressure and collateral flow measured with the krypton 85 myocardial clearance method were determined prior to and fol lowing ligation of the anteroapical epicar dial anastomoses at their midpoints The results of the individual experiments are reported in Table I In summary ligation of the epicardial anastomoses reduced retro grade circumflex arterial flow to 23 per cent retrograde circumflex pressure to 41 per cent and collateral flow to 62 per cent of baseline determinations

Following the ligation of all visualized anteroapical epicardial anastomoses occlu sion of the right coronary artery further reduced retrograde flow and pressure and krypton 85 myocardial clearance rate to the values summarized in Table I These values are comparable to those measured

Table I Chronic preparations—surface collateral and right coronary arterial occlusions

Variables	Exper no	Pao* mm Hg	Pcx/Pao	Retrograde cc/min	Kcx cc/min/100 Gm
Baseline	1	84	0 82	39	
	2	90	0 78	33	
	3	80	0 95	51	
	4	90	0 90	90	67
	5	83	0 92	160	85
	6	88	0 92	120	89
Mean ± S D		85 ± 5	0 88 ± 0 06	82 ± 44	80 ± 9
Surface collateral occlusions	1	85	0 35	7	
	2	82	0 37	19	
	3	90	0 28	10	
	4	85	0 33	21	40
	5	80	0 42	33	56
	6	80	0 38	25	52
Mean ± S D		84 ± 4	0 36 ± 0 04	19 ± 8	50 ± 7
Right coronary artery plus surface collateral occlusions	2	74	0 21	5	
	3	60	0 18	2	
	4	73	0 22	8	24
	5	76	0 30	22	38
	6	70	0 32	14	37
Mean ± S D		70 ± 6	0 25 ± 0 05	10 ± [illegible]	33 ± 6

Abbreviations Pao = mean aortic pressure S D = standard deviation cx = circumflex Pcx = retrograde circumflex pressure Kcx = krypton 85 circumflex myocardial clearance rate time constant
Surface collaterals = anteroapical epicardial anastomoses

in dogs without chronically occluded circumflex arteries (referred to as control dogs in subsequent sections) The mean values of the above mentioned indices of collateral flow measured in control dogs are reported in Table II

Following occlusion of the anteroapical epicardial collaterals and proximal right coronary artery the remaining potential sources of collateral flow would be (1) collaterals arising from the right coronary artery proximal to the site of right coronary occlusion (determined to be negligible on the basis of postmortem right coronary ostial India ink infusions), (2) minute epicardial and mural collateral networks (3) arteriolumininal anastomoses—the work of Gillespie and Love[7] and Prinzmetal and associates[8] has shown these anastomoses to be insignificant in the left ventricle but of considerable magnitude in the right ventricle and (4) extracardiac anastomoses—the surgical procedures undertaken for this study virtually eliminated all possibilities for this source of collateral flow

The mural and minute epicardial collateral complexes of the anterior left ventricular myocardium were qualitatively evaluated by observing the transit of India ink injected into the circumflex arterial cannula following occlusion of the proximal anterior descending and right coronary artery Soon after the circumflex myocardial territory was deeply stained the intense staining of the adjacent anterior descending region was noted to progress toward the central anterior descending zone Brisk antegrade flow of India ink was noted in the coronary veins draining the anterior descending territory and this

Table II Normal (control) dogs

	*Pao** *mm Hg*	*Pcx/Pao*	*Retrograde c c /min*	*Kcx c c /min /100 Gm*
Mean ± S D	84 ± 5	0 19 ± 0 03	3 9 ± 0 5	21 ± 6

Abbreviations P o = mean aortic pressure S.D = standard deviation cx = circumflex Pcx = retrograde circumflex pressure Kcx = krypton-85 circumflex myocardial clearance rate time constant.

probably represented the summation of precapillary anteriolar and venous levels of anastomotic flow Additionally the India ink was observed to appear in the terminal branches of the anterior descending artery and to flow sluggishly in a retrograde fashion without any apparent supply from discrete epicardial conduits Postmortem sections of the anterior descending territory showed the epicardial layers to be more intensely stained than those of the endocardium This disproportion in the perfusion of the epicardial and endocardial zones of ischemic regions has been quantitated by Becker Fortuin and Pitt[9] with the radioactive microsphere myocardial distribution technique (e g the proportion of endocardial to epicardial myocardial microsphere concentrations in the ischemic region was 0 76)

Discussion

The work undertaken for this report involved occluding selected sites of donor coronary arteries and collateral conduits supplying the chronically ischemic myocardial territory of the circumflex artery The retrograde circumflex arterial flow and pressure and krypton 85 clearance rate from the ischemic region were recorded prior to and following occlusive procedures and the contribution to collateral flow by the anastomotic components of the normally perfused arterial systems were estimated

On the basis of post occlusion reductions in retrograde flow the relative contributions to anastomotic flow by the anterior descending and right coronary arteries was estimated to be approximately 90 per cent and 10 per cent respectively

The primary septal artery in the normal dog supplies approximately 10 to 15 per cent of total myocardial flow[10] The contribution of this vessel to anastomotic flow was estimated in one chronic ischemic dog by observing the decrease (2 to 5 per cent) in retrograde circumflex arterial flow following repeated occlusions of the septal vessel Trans septal anastomoses have been shown to be functionally significant in the human coronary arterial system with coronary angiography and as suggested by James[11] may be functionally analogous to epicardial collaterals in that they course along the right ventricular portion of the septum and are presumably relatively free of the highly compressive forces of left ventricular systole

Occlusion of the large epicardial collaterals anastomosing the anterior descending and chronically occluded circumflex artery resulted in significant reductions of all three indices of collateral flow (Table I) but most dramatic was the decrease in retrograde circumflex flow from 82 c c per minute to 19 c c per minute The disproportionately larger reductions in retrograde flow in comparison to the retrograde circumflex pressure and krypton 85 clearance rate may be accounted for on the basis that retrograde flow reflects predominantly the capacity of the interarterial epicardial collateral networks whereas the latter two parameters represent the integral collateral peripheral circumflex vascular system It was noted in this study that the non ischemic antegrade circumflex cannula flow increased by 10 to 20 per cent following occlusion of the anteroapical surface collaterals at their mid points This was interpreted as an indication that the myocardial territory perfused by the cannulated circumflex artery was less than that defined by the epicardial arterial anatomy In line with this observation additional evidence has been obtained in

this laboratory suggesting that the anterior descending arterial territory expands whereas the territory of the circumflex artery decreases following chronic occlusion of the circumflex artery For example, the proportion of anterior descending to circumflex artery antegrade flow was 1 4 in chronically ischemic preparations (9 dogs), whereas the proportion in control preparations (8 dogs) was approximately 1/1 The krypton 85 clearance rates from both anterior descending and circumflex territories perfused antegradely under systemic pressures were in the range of control values, suggesting the difference in the proportion of antegrade flow results from an increase in the territorial mass of the anterior descending artery associated with a decrease in the myocardial mass supplied by the circumflex artery rather than alterations in the peripheral vascular tone of these arterial systems The expansion of the anterior descending arterial territory could be explained on the basis of asymmetrical development of the epicardial arterial bed, or gross alterations in the transitional zone mural vascular architecture or both, resulting from a chronic unidirectional transanastomotic flow and pressure gradient stimulus

Occlusion of the proximal right coronary artery resulted in further reductions of the recorded parameters and the over all results indicate that retrograde flow in canine hearts with chronically occluded circumflex arteries is predominantly delivered by large anterior descending to circumflex arterial epicardial anastomoses (75 per cent) and collaterals arising from the right coronary artery (10 per cent)

In preparations with collateral flows persisting above control values following occlusion of large surface collaterals and the right coronary artery all evidence of collateral flow was virtually eliminated with occlusion of the proximal anterior descending artery The methods employed to monitor collateral flow in this study however, would not clearly reflect continued perfusion of subendocardial regions The fluorescein studies of Prinzmetal and colleagues[8] and rubidium 86 clearance studies of Gillespie and Love[7] have suggested the canine right ventricle is richly endowed with arterioluminal anastomoses whereas the left ventricle is poorly perfused by such routes Such right ventricular arterioluminal anastomoses in the human may account for the rarity of right ventricular infarcts as suggested by Prinzmetal and associates [8] The sparing of subendocardial regions underlying left ventricular infarcts in the human has intrigued many investigators resulting in the hypotheses of simple passive diffusion of oxygen from the left ventricle to the subendocardial regions arterioluminal anastomoses and well-developed subendocardial collateral complexes perfused from the epicardial coronary arteries The latter route has been impressively demonstrated with the stereoradiographic technique of Fulton

The anastomotic flow measured following the large anteroapical epicardial collateral and right coronary arterial occlusions is presumably delivered from the minute epicardial and intramural collateral complexes Observation of the transit of India ink from the circumflex artery to the territory of the occluded anterior descending artery clearly demonstrated the passage of ink into the myocardium veins and retrogradely through the arterial branches of the anterior descending artery without any apparent supply from discrete epicardial conduits

Fulton has demonstrated with his stereoradiographic technique a copious spongiose network of fine intramural vessels intercommunicating with the large vascular elements of a normally perfused coronary artery and an adjacent chronically occluded vessel in both human and canine hearts Such intercommunications exist in normal hearts but to lesser degrees These collateral networks may reasonably account for the persistence of collateral flow following occlusions of the large epicardial collaterals and right coronary artery

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affectin the left side of the body including the face There was hypoesthesia and hypoalgesia over the left s de of the body postural and vibration senses remained intact. Right upper and lower limbs were normal. There was loss of vision in the lower half of the left visual field The right optic fundus was normal the left showed blurring of the superionasal margin of the optic disc with narrowed arteries and veins in the upper half of the fundus the rest of the fundus bein normal Hemorrhages or exudates were not seen. The lungs were clear and the abdomen was normal

The left pyram dal and pinothalamic tract lesions rapidly improved after admission and no residual signs were demonstrated by the next morning He remained well during his stay in hospital without any further attacks His visual field gradually improved over a period of three months and the fundal chan es al o disappeared at the same time

Investigations showed hemoglobin 14 5 Gm per 100 ml packed cell volume 44 per cent white blood count 1? 200 with a differential count of P.L. E.M B. The absolute eosinophil count was 2 4?? per cubic mm Erythrocyte sedimentation rate was 10 mm. the first hour Urine examination showed no su ar with proteinuria from 0 5 Gm to 2 0 Gm. per 24 hours Stool examination revealed a few rhabdit form larvae of strongyloides stercoralis The absolute eosinophil count dropped to 400 per cubic mm. after a course of dithiazanine orally for two weeks for strongyloides infestation. Blood urea was 26 mg per 100 ml creatinine was 0 8 mg per 100 ml albumin/globulin ratio was 3 9/4 0 plasma pro ein electrophoresis showed albumin 40 8 per cent globulin of 8 2 per cent α_2 14 3 per cent β 16 3 per cent γ 20 4 per cent VDRL Rheumatoid factor antinuclear factor and lupus erythematosus cells were negative Chest x ray was normal electrocardiogram (ECG) was within normal limits with mean QRS vector of 0 degrees Metacarpal index was 8 2 Barium swallow showed normal peristalsis with free flow of bar um into the stomach there was no fill n defect nor other abnormalities Trisorb resin sponge uptake of T_3 was normal

B lateral carotid cerebral angiogram was performed and revealed that the left cerebral arteries were filled from the ri ht anterior cerebral by way of the anter or commun cating artery The vascular shadows on both hemi pheres were normal in size and showed no d placement Extracranial port on of the carotids was not visualized Thorac c aortogram and vertebral ang ogram were refused by the patient.

Left temporal artery aneurysmectomy was done under local anesthesia The aneurysm was dissected out in its entire length and resected Postoperative period was uneventful A similar proced re was carried out on the r ght temporal art ry Skin biopsy was taken over the front of the left thigh because of the pec il ar thickening and renal biopsy was done for per i tent proteinuria

Histopathology

Temporal artery aneurysm (Figs 2 and 3) The resected blood vessel is about 1 cm in length At one end the ves el is thickened and dilated No dis ection of vessel wall is seen



Fig 1 Photograph showing patient s right temporal and occipital artery aneurysms Similar aneurysms are present on the left side

There is marked thickening of the intima and media with increase in interstitial mucin like material stained by Alcian Blue The elastica has been completely destroyed and no inflammatory reaction is seen Many collaterals are present in the adventitia Immunofluore cent staining to IgG and thioflavin T for amyloid are both negative

Right renal biopsy (Fig 4) The glomeruli are essentially normal with no increase in cellularity or basement membrane thicken ing and immunofluore cent staining to both IgG and β_1C globulins are negative There are 2 markedly thickened arterioles near the glomerulus with markedly thickened intima and increase in Alcian Blue staining material in the media

Skin biopsy (Fig 5) The epidermis showed features of hyperkeratosis and in the dermis a marked coarseness of the collagen bundles is noted There is moderate increase in elastic tissue with fragmentation of the elastic fibers Inflammatory reaction is absent and there is no increase in inter stitial mucin like material

Case reports

Unusual clinical manifestations of cystic medionecrosis—Report of a case

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Cystic medionecrosis has been a distinct pathological entity since the autopsy studies of Erdheim[1,2] and Rottino[3] The clinical manifestations reported have been either that of dissecting and localized aneurysms of the aorta or aortic insufficiency Hence, diagnosis could only be made from autopsy, or from specimens of aortic aneurysms removed during operation in recent years The purpose of this report is to present a case of cystic medionecrosis involving medium sized arteries and arterioles resulting in unusual clinical features and to give a brief review of the literature

Case report

Y S C a 40 year old Chinese dental technician was admitted as a casualty on July 10 1969 to the University Medical Department of Queen Mary Hospital Hong Kong with sudden onset of left hemiplegia for five hours Five years prior to admission he first noticed a pulsating cord like structure over the left temporal region of the scalp Similar structures were then noticed at different sites of the scalp being most prominent over the frontal and occipital regions Three months before admission he developed an attack of sudden transient dizziness followed an hour later by paralysis numbness and anesthesia over the left side of the body and face There was slurring of speech and deviation of the angle of the mouth to the right He recovered spontaneously six hours later without any residual weakness Since then he had ten similar episodes each lasting from 10 minutes to 6 to 7 hours Each attack was unprovoked and was preceded by a short period of dizziness All the attacks involved the left side of the face and body except for one attack affecting the right arm alone Throbbing frontal headache unrelated to posture or time of the day was sometimes present but never prominent There was no loss of consciousness or disturbances of bladder and bowel

Ten days before admission he experienced dizziness and sudden blurring of vision of the left eye This improved only very gradually and persisted up to the time of his admission

He noticed that his skin was getting coarse dry and progressively rough for the past three years particularly over the front of his thighs

His past health was good and his family history was irrelevant He had farmed in Mainland China for 10 years

Examination showed that he was of moderate body build measuring 160 cm in height and weighing 54 kilograms with an arm span of 160 cm Features suggestive of Marfan s Syndrome were absent He was afebrile, fully conscious and mentally clear with no slurring of speech nor signs of meningeal irritation The skin was generally coarse and was thickened and tight especially over the front of both thighs Joint laxity was absent Two pulsatile vessels with aneurysmal dilatation were found (Fig 1) one on each side of the frontotemporal region with two similar but nonpulsatile cord like structures over the occipital area No tenderness thrill or bruit was detected The pulse was 80 per minute regular and all peripheral pulses were present Blood pressure was 120/80 mm Hg over both upper limbs and 130/80 mm Hg over both lower limbs The heart was not clinically enlarged and auscultation did not reveal any murmurs He was found to have an upper motor neurone lesion

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ride predominantly chondroitin sulphate B and C[10] Manley and Kent[11] presented further experimental studies and suggested that it was due to chondroitin sulphate C In addition large accumulation of dermatan sulphate or heparitin sulphate was found in the media of the resected aortic wall[12] There was no evidence of atheroma or syphilis and inflammatory reaction was absent Although Gore and Seiwert[13] demonstrated the preponderance of elastic degeneration in young individuals in contrast to the predominantly muscular necrosis in older patients both types appeared to be part of the same general disease process[4]

Pathological significance

Pathologically similar accumulation of mucoid material in the media of great vessel had been observed under several circumstances

1 *In normal' aortas* Rottino[3] demonstrated deposits of mucoid material in the aorta of 9? out of 210 routine autopsy cases occurring more commonly in the older age group This agrees with Schultz[14] and Carlson and associates[15] who noted a progressive increase in this material in the senescent vessel

2 *Associated with congenital anomalies* Mucoid material can be found in the media of both normal embryos from 1 to 3 months old and in adults with hypoplastic aorta Thus Costa Florenz[16] suggested developmental disturbance as a cause of the degenerative changes Identical changes were also observed in patients with cardiovascular malformations with right to left shunts[17] but here the primary cause was attributed to tissue anoxia Medial degeneration with destruction of the elastica also occurs in coarctation of the aorta[18] bicuspid aortic valves and calcific aortic stenosis[19] possibly as a result of hemodynamic disturbances distal to the obstruction[20]

3 *Pregnancy* Acid mucopolysaccharide lakes occur frequently in the aorta during pregnancy possibly secondary to hormonal influences[21] This can perhaps explain the greater frequency of dissecting aneurysms in pregnancy than in woman of the control group particularly towards term[22]

4 *Myxoedema* Descriptions on histology of aorta in myxoedema has been few Three patients who developed dissecting aneurysms after total thyroidectomy were found to have mucoid degeneration of the media[23] Another case was presented where histochemical examination revealed presence of acid mucopolysaccharide in the aortic wall of a patient suffering from myxoedema due to chronic atrophic thyroiditis[24]

5 *Marfan s Syndrome* The early changes of the aorta are those of medionecrosis almost indistinguishable from cystic medial necrosis originally described by Erdheim Changes resembling the early ones in the aorta are also found in the pulmonary arteries Specifically peripheral arteries have shown no abnormality but studies in these areas are distressingly few[25]

6 *Rheumatic fever and Hydrala ine syndrome* Pappenheimer and von Glahn[27] recognized changes closely resembling idiopathic medionecrosis occurring in collagen disease states as rheumatic fever Meyer[28] considered that the primary pathologic disturbance was in the amorphous ground substance Hydralazine (apresoline) gives rise to hydralazine syndrome with similar pathological damage of the medial coat This is possibly due to its strong affinity for metallic ions thus resulting in a trace element (probably manganese) deficiency[29] However that the pathology of myxoedema rheumatic fever and hydralazine resembles cystic medionecrosis is not agreed by all pathologists

Clinical significance Although the pathological associations of cystic medionecrosis are very variable its clinical manifestations are not many The clinical features are always a result of weakening of the vessel wall and thus commonly affecting the ascending aorta which is mainly exposed to the distending forces of the left ventricular stroke output.[17]

A review of the literature reveals the following syndromes

1 *Dissecting aneurysms of the aorta*[13 30] and other arteries including basilar[31] left coronary[32] splenic and renal arteries[33]
2 *Local aneurysms of aorta*[4 12 17] and other arteries including hepatic[34] inferior gluteal[35] and subclavian arteries[10]
3 *Aortic valvular insufficiency* which might be functional due to dilatation



Fig 2 Right temporal artery showing narrowed lumen and grossly thickened media and intima (Original magnification ×25 5)



Fig 4 Renal biopsy Two markedly thickened arterioles with normal glomerulus and renal tubules (Hematoxylin and eosin Original magnification ×450)

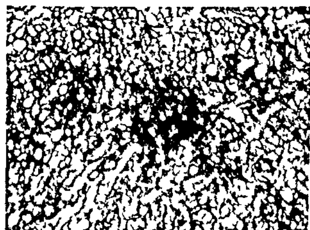


Fig 3 Right temporal artery with cysts of mucin material in the media and intima stained by Alcian Blue (Alcian Blue stain Original magnification ×450)



Fig 5 Skin biopsy Moderate increase in elastic tissue and fragmentation of elastic fibers is seen in the dermis (Weigert s stain Original magnification ×105)

Discussion

Wiesel[5] in 1906 first described medial changes of blood vessels in non syphilitic young persons dying shortly after the onset of fulminating infections This was probably the first description of medionecrosis Since then various degenerative changes of the media have been reported including cyst like areas filled with "gelatinous material,"[6] scattered foci of "fatty degeneration"[7] and hyaline degeneration of interlamellar connective tissue[8] However, these latter types of degenerative changes were not supported by subsequent reports It was Erdheim[1,2] who described the specific lesion in the medial coat of aorta as a focal accumulation of basophilic homogeneous material Thus it has been known as *Erdheim s medionecrosis* or *medionecrosis aortae idiopathica cystica* and has been considered to be a distinct pathological entity[2]

The histology in described cases consisted of intimal thickening due to proliferation of fine collagen fibers separated by pale myxomatous tissue The elastic lamellae were very variable but were often split and fragmented separated by irregular cystic spaces containing basophilic amorphous material staining positively for connective tissue mucin with Alcian Blue preparation[9] This was believed to represent collections of acid mucopolysaccha

eralized mesenchymal disorder In fact Goodman and colleagues[44] reported a case of combined Ehler Danlos and Marfan s Syndromes

Erdheim s medionecrosis or Marfan s Syndrome That this patient had medionecrosis of blood vessel was established by biopsies Medionecrosis can be associated with many conditions (Marfan s Syndrome myxoedema pregnancy etc see above) and has been produced in experimental animals by a number of techniques including lathyrism[46-47] pyridoxine deficiency[48] and copper deficiency[49] The mucoid component of the degenerative process merely represents one aspect of the body reaction[50] Whether this patient has Marfan s Syndrome is highly debatable Clinically there were none of the stigmata characteristic of this syndrome and family studies are impossible because the other members of his family are living in Mainland China However this can still be Marfan s Syndrome for there are undoubtedly cases where aortic medionecrosis occurs without skeletal and ocular changes[26] Together with the skin changes observed in this patient we believe that this is a formes frustes of Marfan s Syndrome rather than Erdheim s medionecrosis alone It is also believed that many cases of Erdheim s medionecrosis may be an incomplete form of Marfan s Syndrome[51 53]

Summary

Although cystic medionecrosis of great vessels has been a well known pathological entity the diagnosis is usually made at autopsy The clinical manifestations are often limited to the aorta resulting in aneurysms and aortic insufficiency Report is given of a case where the degenerative process involves medium sized arteries and arterioles giving rise to multiple aneurysms of the extracranial arteries transient cerebral ischemia persistent proteinuria and retinal involvement associated with skin changes Different pathological conditions where medionecrosis occur are reviewed The relationship between Erdheim s idiopathic cystic medionecrosis and Marfan s Syndrome is briefly discussed

We wish to thank Dr W C Chan Department of Pathology Queen Mary Hospital Hong Kong for histological studies.

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of the aortic ring or with direct medionecrosis of the aortic valve[36]

4 *Rupture of the aorta due to thinning*[37]

To the above we would like to add five other clinical features as illustrated by the patient here presented, i e ,

1 *Multiple aneurysms of the extracranial arteries* Aneurysms of the temporal artery are rare Non traumatic aneurysms of the occipital artery must be exceedingly rare as 90 per cent of cases of temporal artery aneurysms were traumatic in origin The others were considered arteriosclerotic, unclassified, and doubtful[38] Guida and Moore[39] were able to find only 111 reported cases of aneurysms of the temporal artery in the literature up to 1968 Hagstrom and colleagues[40] subsequently reported five more cases and considered that there were only 130 cases up to that time It was unfortunate that the histological descriptions were usually not given in greater detail

The present case assumes significance not only because of its rarity but also because, to the best of our knowledge, this is the first reported case of temporal artery and occipital artery and in fact multiple extracranial artery aneurysms due to cystic medionecrosis

2 *Transient cerebral ischemia* The repeated attacks of transient hemiplegia and facial paralysis with spontaneous complete recovery within a few hours suggest a vascular lesion Judging from the marked distensibility and smoothness of the vessel wall when the resected temporal artery was examined, it is not surprising that the vessels should appear normal in angiograms even when mucoid degeneration was present However since the origin of the common carotid and vertebral basilar arteries were not visualized in the cerebral angiogram a lesion in the extracranial portion of the carotid or vertebral basilar artery which could also account for the transient ischemic episodes cannot be entirely ruled out

3 *Renal involvement* The persistent proteinuria which varied from 0 5 to 2 Gm per day prompted us to do a renal biopsy That vessels as small as the arterioles could be involved was a surprising finding This could only mean that possibly all the vessels in the body, from the aorta to the arteriole, took part in the degenerative process, in contrast to the results of Milne and associates[41] who found that in their case the degenerative process did not extend into the branches of the aorta

4 *Retinal involvement* The retina changes are possibly due to thrombosis or emboli of a branch of retinal artery Although unlike the renal changes histological proof of involvement of the retinal vessels is lacking it may be assumed that they were involved in a manner similar to the renal arterioles unless embolization from extracranial arteries is again incriminated This again suggests that medial degeneration is a generalized process rather than being limited to the aorta

5 *Skin changes* Skin changes associated with idiopathic cystic medionecrosis have never been described However skin changes occurring in Marfan's Syndrome had been reported occasionally These include scanty subcutaneous fat laxity of ligaments scaly areas of the feet and hyperkeratosis of the toes elastoma like lesions and acrosclerosis[42] The histopathology of the skin biopsy in this patient is most peculiar in that there is presence of coarse collagen bundles and fragmentation of the elastic fibers Histologically this would suggest Ehlers Danlos Syndrome although clinical support from hyperelasticity of the skin is lacking A recent clinical and histological study of the skin of 10 patients with Marfan s Syndrome by Moretti and co workers[43] revealed changes very similar to or identical with those in Ehlers Danlos Syndrome but with less marked hyperelasticity in the former group of patients Hence the skin changes in this patient need not be exclusive of Ehlers Danlos Syndrome, but form part of the clinical picture of a gen

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Review of the literature reveals the number of cases of congenital subclavian steal to be rapidly increasing indicating that the occurrence is not as rare as previously thought Our case demonstrates that the congenital subclavian steal may present in the newborn period and can be easily diagnosed It discusses the typical clinical signs one might expect to encounter and describes the early development of collateral pathways This review should alert the clinician to the associated cardiovascular lesions and present a glimpse of the natural history of the defect with a view toward timely surgical intervention

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When this 3 600 gram newborn developed severe congestive heart failure at 15 days of age he was transferred to Johns Hopkins Hospital for definitive cardiac evaluation.

On physical examination he was a dusky infant with marked tachypnea The pulse rate was 156 per minute and the respirations were 80 per minute A discrepancy was noted in both the blood pressure determinations and the pulse amplitudes The right arm and leg pressures were 100 65 mm Hg and the left arm was 80/60 mm Hg The left brachial and radial pulses were indistinct to palpation The precordium was hyperdynamic and there was a gallop rhythm The first heart sound was normal and the second showed pulmonary accentuation Neither a bruit nor a murmur was noted on auscultation. Gross hepatomegaly was found without evidence of splenic enlargement Neurologic examination was normal

The initial electrocardiograms (ECG s) showed biatrial enlargement and right ventricular hypertrophy with an indeterminate axis There was right ventricular enlargement and pulmonary plethora on the chest film with a small posterior indentation of the esophagram.

Cardiac catheterization was performed after 48 hours of successful anticongestive therapy The hemodynamic data revealed a large ventricular septal defect with elevated pulmonary arteriolar resistance The cineangiocardiogram demonstrated a ventricular septal defect and a right aortic arch The left and right common carotid arteries were the first brachiocephalic branches (Fig 1A) These were followed by the right subclavian artery which gave off the right vertebral and internal mammary arteries (Fig 1B) A blind diverticulum opacified on the distal arch (Fig 1C) Although the proximal left subclavian artery could not be identified filling of the distal left subclavian artery took place in a

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Fig 1 A through D A Retrograde right subclavian arteriogram in the LAO position revealed the left (LCC) right common carotid (RCC) and right subclavian arteries (RSC) respectively B Origin of the right internal mammary (RIM) and tortuous vertebral (RVA) arteries from the right subclavian (RSC) C A conspicuous descending aortic arch diverticulum (D) was noted in the absence of proximal left subclavian filling D Late phase retrograde filling of the distal left subclavian (LSC) and internal mammary arteries (LIM) by way of the left vertebral artery (LVA) The blind stump of the distal subclavian approximated the level of the diverticulum

retrograde fashion by way of the left vertebral artery Both the left subclavian and internal mammary arteries could be seen in the late frames of the cineangiogram (Fig 1D)

By 18 months of age a barium study continued to show a conspicuous posterior indentation (Fig 2) while roentgenograms of the upper extremities were normal Reassessment of the blood pressures revealed a right arm pressure of 100/70 mm Hg leg pressures of 120/70 mm Hg and 90/70 mm Hg in the left arm

Recatheterization in preparation for definitive cardiac surgery showed a large left to-right shunt at the ventricular level with slight elevation of the pulmonary arteriolar resistance Biplane aortography again revealed the right aortic arch and clearly



Fig 2 Lateral esophagram illustrates left atrial enlargement and a posterior indentation caused by the aortic diverticulum



Fig 3 *A* and *B* *A* Anteroposterior view *B* Lateral view Antegrade aortogram revealing a mirror image right aortic arch with left (*LCC*) right (*RCC*) common carotid and right subclavian (*RSC*) arteries in sequence A prominent diverticulum (*D*) opacified on the descending arch followed by an unusual collateral artery (*CA*) The proximal left subclavian artery failed to visualize

allowed definition of the left common carotid artery as the first vessel followed by the right common carotid and right subclavian arteries respectively On the distal arch a prominent blind diverticulum opacified and an unusual collateral artery was visualized reaching for the left arm (Fig 3) Careful examination of the late phase films in the region of the left clavicle revealed retrograde filling of the left subclavian artery by way of the left vertebral artery and thyrocervical trunk (Fig 4)

A supracristal ventricular septal defect was successfully closed at open heart surgery No intervention was deemed necessary for the obliterated proximal subclavian artery The patient has done well since surgery

Discussion

The subclavian steal phenomenon was first described by Contorni[1] in 1960 When the proximal portion of the subclavian artery was obstructed retrograde blood flow occurred in the ipsilateral vertebral artery into the low pressure distal subclavian system Soon afterwards Reivich and associates[2] reported a clinical syndrome produced from occlusion of the proximal subclavian artery Blood siphoned from the basilar area of the brain by the vertebral artery produced symptoms of cerebral insufficiency[3,4] The combination of hemodynamic phenomena and clinical symptoms was descriptively designated the Subclavian Steal Syndrome in honor of the piratical subclavian artery[5]

While atherosclerosis is by far the most



Fig. 4. Magnified left cervical clavicular area with retrograde filling of the left subclavian artery (*LSC*) by way of the left vertebral artery (*LVA*) and the thyrocervical trunk (*TT*).

common cause,[3] other etiologies have included thrombus formation[6] as well as spontaneous emboli from the left heart[7] or following trauma.[8] Folger and Shah[9] reported 12 cases following Blalock-Taussig anastomosis when the vertebral artery was left intact. Bloodwell and colleagues[10] described it during bypass with failure to perfuse the subclavian artery, and others inadvertently created the syndrome. Intrauterine acquired diseases such as the hypercalcemic syndrome may also cause proximal subclavian obstruction.[11-14]

The 26 cases of angiographically documented congenital subclavian steal gleaned from the literature are summarized in Table I. Seventeen cases occurred with a right aortic arch and nine with some form of interruption of a left aortic arch. The point of interest is that those patients with a left aortic arch usually have a coarctation or total interruption of the aorta involving the origin of the subclavian, whereas patients with a right aortic arch often have only a localized hypoplasia, atresia, or isolation of the subclavian artery itself with a normal aortic arch.[20,32,3] A comprehensive study of the embryologic patterns has been published[32] and the anatomic potentials for a subclavian steal outlined in great detail by Becker and co-workers.[3]

When the subclavian artery arises distal to the coarctation instead of being directly included in the constriction, then blood flow to the lower extremity may be supplied in retrograde fashion through the vertebral subclavian system, a condition referred to as a "subclavian aortic steal."[28] Bilateral subclavian aortic steals have been observed in patients with interruption of the aortic arch when the left subclavian and anomalous right subclavian arteries empty distal to the aortic obstruction.[13,23,31] As evidenced by our own experience, there are many more steals with coarctations and interruptions than have been reported.

Classic neurologic symptoms have never been seen in a newborn patient and are rarely described in childhood. Only 5 patients with the congenital subclavian steal were clearly noted to have associated complaints during childhood.[13, 3, 5, 33] The youngest patient was 11 years old at the time of onset.[13] Complaints are usually confined to paresthesias and exercise intolerance of the ipsilateral arm. Cerebral symptoms have not been seen in early childhood. Neurologic expression depends on the delicate balance between the siphon and other collateral circuits supplying the ipsilateral extremity.[27] The development of additional extracranial collateral channels in utero and the absence of atherosclerosis are thought to be the main reasons for the lack of symptoms in childhood.[20] This would indicate that elective surgical intervention should not be considered before the second decade at the earliest. Repair shortly before the onset of adolescence should avoid growth retardation of the ipsilateral extremity. Fortunately, the anatomy is much more amenable to reconstructive surgery by that time.

Classical collateral pathways involving the internal and external carotids, cervicals, thyroids, occipitals, vertebrals, muscular branches of the vertebrals, epigastrics, and intercostals are frequently identified by angiography even in childhood.[20,38,39] Several collateral pathways were well established in our patient before a year of age. Besides the vertebral artery and thyrocervical trunk, a prominent right internal mammary artery communicated with the left subclavian by way of the intercostal system. The unusual collateral artery distal to the diverticulum (Fig. 3) is similar to that described by Abrams[40] in a patient with coarctation of the aorta. The ability of the infant to form early extensive collateral circuits is no longer in question. The parallel process has been well documented in infants with coarctation of the aorta.[41]

The pooling of data revealed that pa-

Table I Summary of cases of angiographically documented congenital subclavian steal syndrome

Author and year of study		Age (yr)	Aortic arch	Coarct*	Sx	Comments
1 Vianna[15]	1954	18	L	+	0	
2 Massumi[16,34]	1963	6	R	0	0	Right cervical arch
3 Daves[17]	1964	3/12	L	+	0	VSD PDA
4 Bosniak[1]	1964	?	L	+	0	Bilateral subclavian steal
5 Grollman[19]	1964	43	L	+	0	
6 Stewart[20]	1964	17 days	L	+	0	VSD ASD hypoplastic aortic isthmus bilateral PDA
7 Pillsbury[21]	1964	16	L	+	0	Interrupted aortic arch
8 Levine[22]	1966	33	R	0	+	
9 Bradley[23]	1966	21	R	+	+	
10 Antia[24]	1966	6	R	0	0	Supravalve aortic stenosis
11 Antia	1966	12	R	0	±	
12 Gerber[12]	1967	8	R	0	0	Hypercalcemic syndrome
13 Zetterquist[25]	1967	10	L	+	0	Interruption aortic arch bilateral subclavian steals
14 Replogle[26]	1968	2	R	0	0	Tetralogy of Fallot
15 Lansing[27]	1968	6	R	0	0	Tetralogy of Fallot
16 Lansing	1968	3/12	R	0	0	Tetralogy of Fallot
17 Love[8]	1968	30	R	0	+	
18 Maranhao[29]	1968	19	R	0	0	
19 Skalpe[30]	1969	7	R	0	0	Tetralogy of Fallot
20 Grossman[3]	1969	14	R	+	0	
21 Villar[3]	1969	11	L	0	+	Supravalve aortic stenosis
22 Victorica[32]	1970	2	R	0	0	Tetralogy of Fallot
23 Victorica	1970	2/12	R	0	0	VSD PAPVR
24 Shuford[33]	1970	23	R	0	+	
25 Shuford	1970	34	R	0	0	
26 Morgan[34]	1970	19	L	+	0	Interruption aortic arch bilateral subclavian steals
27 Pieroni	1972	15 days	R	0	0	VSD

*Abbreviations ASD = atrial septal defect Coarct = coarctation of aorta L = left R = right Sx = symptoms PAPVR = partial anomalous pulmonary venous return PDA = patent ductus arteriosus VSD = ventricular septal defect

tients with a congenital subclavian steal have a higher incidence of associated cardiovascular defects When found in conjunction with a left arch and coarctation lesions are confined largely to either a patent ductus arteriosus and/or a ventricular septal defect[4] whereas defects with a right arch depend on the particular type of right aortic arch Several authors[43-45] have firmly established the connection between intracardiac defects and a mirror image right aortic arch Although the number of cases was small this correlation was observed in the literature reviewed by us Tetralogy of Fallot was the most common lesion found with a mirror image right arch (Table I) Prediction of an associated congenital heart lesion may be made upon identifying the orientation of the aorta with respect to the esophagus A retroesophageal right aortic arch produces a wide concavity on the barium filled esophagus This is not to be confused with the smaller indentation made by an anomalous right subclavian artery from a left aortic arch[32] Therefore a barium study proves to be an invaluable diagnostic aid in patients with a right aortic arch

Careful examination of both brachial pulses as well as the femorals should be performed routinely on every newborn infant suspected of having congenital heart disease In the presence of a right aortic arch this simple maneuver may be particularly rewarding A perceptible difference in the brachial pulse amplitudes should alert the clinician to the possibility of a subclavian steal



Fig 4 Magnified left cervical clavicular area with retrograde filling of the left subclavian artery (*LSC*) by way of the left vertebral artery (*LVA*) and the thyrocervical trunk (*TT*)

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When aortography is performed in a patient with tetralogy of Fallot and a right aortic arch, attention should be focused upon the mode of filling of the left subclavian artery as well as the specific anatomy of the brachiocephalic vessels Failure to recognize the existence of an atretic proximal left subclavian may eventuate in a futile attempt at a Blalock Taussig anastomosis with little hope for another palliative procedure from the left thoracotomy approach

Summary

This report is a reminder that the congenital subclavian steal can occur in the newborn and can be diagnosed clinically Increased awareness of the phenomenon has been partially responsible for the recognition of 26 cases since the first described in 1960 This would indicate that the entity is not as rare as previously thought

Careful palpation of both brachial pulses as well as the femorals should be performed in all newborns, especially in infants with a right aortic arch or coarctation of the aorta A discernible brachial pulse discrepancy should alert the clinician to the possibility of a subclavian steal

While associated cardiovascular lesions are not uncommon neurologic symptoms are infrequently seen in early childhood Extensive extracranial collaterals and the absence of atherosclerosis are thought to be the main reasons for the lack of symptoms in childhood Elective surgical intervention is, therefore, not usually necessary before the second decade

The authors wish to extend thanks to Dr L Haroutunian and Mrs D Mitchell for their aid in preparing the manuscript

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should include a careful evaluation of the state of the heart blood vessels brain and kidneys along with the usual investigations necessary to learn the state of health as prompted by a detailed history and careful and thorough physical examination

Examination of the eyegrounds electrocardiogram roentgenographic studies renal function tests (PSP concentrating ability careful urine analysis urea and creatinine clearances intravenous pyelogram) as well as the minimal hematologic studies blood chemistries and other procedures only considered *necessary* should be performed

Unfortunately patients are funnelled through routine or screening investigations and complete renal studies without individualization Any patient who enters a physician s office is *one person* and not a group to be managed on a statistical or epidemiologic basis or by general rules of study or therapy Each patient is different and each must be approached in a manner most effective for him This is too frequently forgotten

It is not possible in this short presentation to discuss in detail the indications and limitations of more modern methods for studying a patient s kidneys for renovascular hypertension A careful clinical study as outlined above with a few properly performed urinalyses PSP (2 hours) concentration tests and careful intravenous pyelography will be adequate for over 95 per cent of patients with arterial hypertension From the results of these studies and the clinical data the physician will know if further studies are necessary Since urea and creatinine levels in the serum are so routinely ordered (unnecessarily so) the physician may wish to determine simultaneously the 24 hour urea and creatinine clearances to take most advantage of these routine blood studies Unilateral or separate renal studies by retrograde catheterization and pyelography may be necessary when unilateral renal disease is suspected However many such studies are interesting and fashionable but not necessary for good therapy certainly not in every patient with hypertension It is much more important to measure the 24 hour loss of protein and water in the urine along with several carefully and properly performed daily urinalyses Urinalysis is not only neglected but frequently improperly done and not thoughtfully considered or understood

Initial therapy

Once the clinical study is completed the physician knows the therapeutic approach he should outline initially For example if all cardiovascular studies are normal and the patient presents a history of hypertension for many years the physician knows that the hypertension is mainly psychogenic in origin and that certainly the patient s blood pressure is *normal* when he is sound asleep A continuously elevated blood pressure for many years should produce detectable structural and/or functional changes in some organ systems Therefore if such changes are absent the patient s blood pressure must be normal when he is relaxed and undisturbed Furthermore from the outset it is evident that such a blood pressure can be readily reduced to normal with the use of little medication

Such a patient will require little if any ganglion blocking agents If the patient s history and other clinical data warrant further investigation then the patient should be studied for pheochromocytoma renal artery obstruction pyelonephritis or whatever is indicated If the hypertension is malignant the patient may be and should be admitted to a hospital when possible for initial therapy and closer observation and for further studies if necessary and possibly for careful use of the extremely potent antihypertensive drugs If the diagnosis is benign essential hypertension the patient can be treated equally well if not better at home with visits to the physician s office The patient s wife or husband or other person who will be responsible for the patient should be present when therapy is outlined in absolute detail If the instructions are carefully presented initially much time will eventually be saved and the results will be most gratifying

Fundamental measures

The basic therapeutic measures are most important and should be carefully outlined and explained in detail to the patient and to a responsible understanding devoted and adequately motivated member of the family

Rest The patient should be meticulously

Special article

Management of benign essential arterial hypertension

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The most important advancement in the field of hypertension from the viewpoint of the patient and clinician is the development of the many antihypertensive drugs by the pharmaceutical industry Because of the introduction of antihypertensive agents just a few years ago, a physician now can approach his patient with hypertension with confidence that he can reduce the blood pressure to normal There is no doubt that the introduction of these drugs represents one of the most important achievements in therapy of cardiovascular disease for all times In fact few people should die of hypertensive disease today Now that potent drugs are available to reduce arterial hypertension it behooves the physician to learn to employ these agents most effectively For with proper use of these drugs a patient s blood pressure can be maintained at almost any level desired Unfortunately the more recent discussions and reports on the surgical management of renovascular and adrenocortical hypertension have confused many clinicians who fail to realize that the number of patients with arterial hypertension whose elevated blood pressure is amenable to surgery is extremely small Because of this too many physicians have lost sight of the fact that by far the greatest majority of patients with hypertension require medical therapy Furthermore if renovascular hypertension does exist in certain patients and the objective is to reduce the blood pressure to normal the blood pressure can even be reduced to normal in almost all such patients by good medical management

Unfortunately it is not possible in a presentation of this sort to justify or support every procedure used in treating patients Thus only some of these procedures are expanded upon here For most effective therapeutic results the physician should have adequate knowledge of the action of the drugs and other agents available and certainly of those agents that he uses in therapy

Inventory of health

Obviously before proper therapy can be introduced the physician must know in detail the entire state of health of his patient, including physical and mental health He must determine not only the diagnosis of the type of hypertension but also the state of the entire cardiovascular cerebrovascular and renal systems Many patients have multiple diseases all of which influence the cardiovascular system as well as therapy and the approach to the best therapeutic results The medical study

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should include a careful evaluation of the state of the heart blood vessels brain and kidneys along with the usual investigations necessary to learn the state of health as prompted by a detailed history and careful and thorough physical examination

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The basic therapeutic measures are most important and should be carefully outlined and explained in detail to the patient and to a responsible understanding devoted and adequately motivated member of the family

Rest The patient should be meticulously

queried concerning problems that may be producing psychic stress No matter how minor, these must all be solved or rationalized The patient should be instructed to rest physically and mentally Initially, he should retire early at night remain in bed late in the morning and rest for an hour or two after noon meals Psychic stresses should be avoided the patient should relax and "loosen up He should avoid arguments unpleasant duties, civic activities family problems, serious business discussions or ventures, and physical activity except for walking slowly and relaxed He can conduct himself in a relaxed and non tense manner and be as successful in business or even more so with training and assistance from his physician Instructions must be discussed and defined in detail, not merely passed over with a statement of "take it easy " Such a statement is not only vague but always ineffective

Basal blood pressure levels Home recording of blood pressure is *indispensable* for satisfactory therapy It is no more reasonable to expect to regulate the patient s blood pressure without home recordings of the blood pressure than to expect to regulate a patient s diabetes with insulin without observing the urine for sugar at home Furthermore the blood pressure obtained in a doctor s office is often increased by the examination the office surroundings and the patient s apprehension and reaction to the doctor Incidentally a physician who chronically elevates patients blood pressures needs to evaluate his manner with and approach to patients The physician should have a soothing rather than an excitatory influence on his patients Nevertheless home recordings can clarify problems for the doctor as well as for the patient

Physicians often object to having their patient's blood pressure recorded at home If properly handled the practice causes no difficulties and is most rewarding The patient is advised to learn what factors elevate his pressure as well as those factors conducive to low blood pressure levels The patient should then avoid the former and favor the latter Furthermore the patient and his family will learn about the variability of arterial blood pressure In fact every home should contain a mercury type blood pressure recorder just as it contains a thermometer

The patient should not record his own blood pressure Squeezing the blood pressure bulb elevates blood pressure to a variable extent An intelligent reliable and devoted member of the family should record the pressure several times a day as it seems advisable and as curiosity demands Records should be maintained and copies mailed or delivered to the physician periodically Notes of medication, activities symptoms and other points of interest should be kept daily very much like nurses notes in a hospital chart A quick glance at these records makes it possible for the physician to learn not only the basal level of the blood pressure but also the variations and possible causes for them pharmacologic responses to drugs the patient s surroundings and activities and symptoms such as anginal pain headache, palpitation fatigue, dyspnea, and the like From these records the physician can readily and correctly vary drugs and other therapeutic measures as required

It is surprising how many patients blood pressures return to normal at home without the use of the more potent antihypertensive drugs

The patient is advised to buy a good mercury type manometer with a Velcro cuff and a simple bell type stethoscope Both can be purchased for about $50 00 A dependable member of the family is taught to use the apparatus This can be done by a nurse or technician in a few minutes

Diet The patient should lose weight slowly (4 to 6 pounds per month) if he is overweight He should be advised to do so voluntarily by eating less of a well balanced diet and watching his weight changes by regular weighing A reduction diet may be given if necessary He should eat lots of fruit and vegetables, almost becoming a vegetarian He should eat small meals slowly and relaxed He should avoid heavy beef and ' red meats He may have an occasional egg and should depend more on broiled seafood and fowl Skimmed milk and cottage cheese but no dairy fats should be used He should not eat pork in any form and should have minimal amounts of condiments and spices He should avoid salty foods and not add extra salt to his food Salting should be limited to the level used for cooking for the family or a little

less He should have a fluid intake to assure urine volume of about 1 000 to 1 500 ml per day This diet should be modified only as necessary for special clinical reasons

The patient should be advised to stop the intake of all caffeine beverages and alcohol except for an occasional alcoholic beverage for its tonic effects and to discontinue the use of tobacco

Sedation Sedatives should be used as necessary to assure relaxation and sleep Phenobarbital can be taken in amounts to meet the patient s own needs and not at a routine dose Some patients require about 4 to 5 grains (240 to 300 mg) per day The dose can be varied by the patient and the responsible member of the family Seconal 100 to 200 mg may be used at bedtime The physician may use any other well-established drugs to suit his particular patient s responses

Rauwolfia serpentina (whole root) is very useful Raudixin 100 mg 3 or 4 times a d v is an excellent preparation The drug not only has a tranquilizing effect but tends to reduce blood pressure and slow the heart rate The patient must be advised to watch the response of his blood pressure to the drug and to reduce the other sedatives as well as the Raudixin as necessary to avoid excessive sedative and hypotensive effects However hypotensive seizure from Raudixin is extremely rare I have never seen it The patient must be warned that the full effects of the drug may not be reached until 3 to 6 weeks after beginning this medication At that time only 1 tablet (100 mg or less) once or twice a day may be sufficient Fifty mg tablets should be used when smaller doses are required The patient must also be warned of its undesirable side effects —i e congestion of the nasal passages depression nightmares and greater sensitivity to cold or cool environments The nasal congestion becomes less troublesome with time If the depression or nightmares become marked the dose of the drug should be reduced or discontinued at times It is better not to mention to the patient the impotence produced by this and by other antihypertensive drugs in order to avoid apprehension or the production of psychogenic impotence or interference with the patient s willingness to use the necessary drugs

The average mild hypertensive state usually requires no further medication Associated diseases should be treated such as periodontoclasia chronic prostatitis and chronic constipation and improper dietary and personal habits and hygiene should be corrected

After a few days on the regimen outlined above the home recordings of blood pressure will indicate the response to therapy and the regimen the basal levels of blood pressure and the patient s attitude If his blood pressure is found to be declining the regimen is not varied In most instances a normal level will be reached in two to three weeks if the physician works diligently with the patient This will please the patient and family so that therapy will be followed even more enthusiastically

More potent antihypertensive drugs

Should the blood pressure not decline sufficiently or if it was very high originally more potent drugs may be added as required Included among these are the thiazides or furosemides and if necessary so called sympathetic blocking agents There are many preparations available in these groups of drugs The physician will find it better to select one of each group and become thoroughly acquainted with it rather than to change to a new one as soon as it becomes available and before it is found to be superior to any that are already in use A change should be made only when necessary and when well-established advantages become evident

Diuril Diuril (Chlorothiazide) is a good preparation among the thiazides and is the original thiazide A tablet (500 mg each) may be given once twice or three times a day and the dose varied in accordance with the patient s response Its kaliuretic naturetic and local vascular effects are probably responsible in large part for its antihypertensive action Once a patient is receiving a thiazide he should be observed closely and continuously The drug can produce serious electrolyte disturbances even fatal cardiac irregularities It makes elegant digitalization and its regulation most difficult and probably impossible However it is extremely useful especially in uncomplicated arterial hypertension but it must be used judiciously and properly As the blood pressure declines the dosage

should be gradually reduced and even discontinued entirely

Sympathetic blocking agent Among the sympathetic nervous system blocking drugs guanethidine (Ismelin) is a good one Even though the precise action of the drug is not yet entirely known, it is most effective This drug is added to the above therapeutic regimen later if necessary or initially if the blood pressure is extremely high and malignant The drug is given in the morning as a single dose, starting with 2 5 mg and increasing the dose in increments of 2 5 to 5 mg per day until the desired effects are obtained It is excreted and metabolized relatively slowly, so that in some patients there may be a residual amount accumulated each day Rarely is it necessary to exceed 25 mg per day if the above outlined therapy is properly and carefully explained and discussed with the patient and his family and is followed closely

The patient should be warned of the syncopal action of these drugs Giddiness weakness, fatigability, and slight sweating are among the early manifestations of excessive dosage When these symptoms appear the patient should have his blood pressure checked frequently in the lying sitting and standing positions He should be instructed to vary the drug accordingly and notify his physician of findings and certainly of difficulties when encountered When he feels faint he should lie down until the action of the drug subsides and his physician is contacted

As the blood pressure declines, the dosage of the more potent drugs should be reduced and these drugs eliminated first The basal or fundamental therapeutic measures should never be eliminated greater freedom in activity (always carefully monitored by blood pressure recordings) may be allowed when the blood pressure declines to normal It is interesting how much the drugs may be reduced or even discontinued and still have the blood pressure remain normal once it has reached normal levels The patient should have his blood pressure checked at home from time to time and he should see his doctor regularly so that drugs may be reintroduced promptly when the blood pressure begins to rise

There are, of course, physicians who employ different drugs and even sympathectomy The latter procedure is rarely, if ever, indicated Each physician has his own regimen Therapy must be effective and should *not injure* the patient Surgical sympathectomy is not necessary Even renovascular hypertension can be reduced to normal by medical means The antihypertensive drugs have greatly reduced the morbidity and mortality from arterial hypertension [1]

Blood pressure of all patients should be reduced to normal levels regardless of the magnitude of elevation, even if the elevation is slight Only the less potent drugs and often only the basal therapeutic procedures such as psychic and physical rest and diet, discussed above will be needed for patients with mild hypertension It appears that hypertension and the aging process are two extremely important factors responsible for the pathogenesis of arteriosclerosis in man The former can be controlled and should be if one wishes to control the rate and extent of development of arteriosclerosis

The patient s blood pressure must be reduced much more cautiously and less rapidly in the presence of ischemic heart disease renal insufficiency or marked impairment of renal function or cerebral arteriosclerosis with cerebral ischemic disease These complications are all special problems which deserve serious consideration The physician must not have a fatalistic attitude about the treatment of hypertension The above clinical states can improve with gradual reduction in blood pressure even though the improvement is slow in some instances The response of the involved vital organs (heart brain, and kidney) must be carefully observed and must be tested by cautious and slow reduction in blood pressure especially when the pressure is high and the respective organs are already diseased These and many other important problems are encountered but are not always insurmountable Uremia with chronic renal disease and irreversible loss of renal function offers the greatest difficulties in the management of hypertension as is well known

With the use of blood pressure recordings in every home, just as the use of the clinical thermometer is common in every home hypertension can be detected early and

proper treatment instituted before irreversible damage to organ systems occurs. Very few people should die of hypertension today. Early detection of abnormal elevations of arterial blood pressure is imperative if we expect to eliminate the fatalities and ravages of hypertension. And home recording of blood pressure is indispensable for this.

The therapeutic regimen briefly outlined above is intended for the large majority of people with high blood pressures. Obviously, there are special hypertensive states which require special diagnostic and therapeutic approaches, but these are relatively uncommon. After all, it is only proper to learn to treat the large majority of hypertensive patients properly first and prevent the appearance of the terminal and irreversible hypertensive disease states rather than to focus attention on these latter disease states which should be preventable.

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Review

Myocardial infarction in young people—Experience in U S.S.R

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It is the consensus of Russian cardiologists that myocardial infarction (MI) in young people i e under 40 years of age, is not rare and that in the past two decades its incidence has increased faster than in the older population [1-5] However, we were unable to find adequate epidemiologic data to show a statistically significant difference in the trend of myocardial infarction in the different age groups in U S S R In Klimenko and Lyba s[2] sample of patients under 40 years of age with myocardial infarction only 6 cases occurred within the first period of 7 years and 50 cases during the second period of 7 years of a total of 14 years of observation This would be indeed a fantastic acceleration of prevalence The sample is much too small for a definite conclusion the difference between the two 7 year periods may be due to differences in sampling Hospital admission statistics have limited significance for analysis of age dependent trends of prevalence Nevertheless the quite general opinion of Russian cardiologists from widely separate areas that the incidence of MI in young patients is increasing probably has some realistic background, although valid epidemiologic statistical evidence is not yet available to the best of our knowledge * In the United States the percentage of the age group 25 to 35 in the total mortality from atherosclerotic heart disease does not show any increase from 1950 to 1967, there is a slight increase in the age group 35 to 39 and a pronounced increase in the age group 60 to 69 (United States vital statistics)

During the past two decades MI in patients under 40 years has been of increasing concern to Russian cardiologists as evidenced by the large number of publications Gurevich[6] in his recent (1970) condensed review quotes 84 Russian references the majority published in the sixties Since we are here concerned with experience in U S S R references to comparable Western literature are few

While Russian authors are quite unanimous regarding the relative frequency of MI in young patients there is a considerable discrepancy as to clinical course and symptoms mortality rate preinfarct history complications etc The discrepancy is largely explained by the small sample size in most of the observations and by the lack of statistical evaluation

Criteria

The Russian authors differentiate between micro and macro MI In the literature accessible to us we were not able to find precise pathologic, clinical, or electrocardiographic criteria for this differentiation It appears that abnormal Q waves are

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*Table I Incidence of various features of MI in per cent (mean and S D) in 120 patients under 40 years and 120 patients over 60 years and statistical significance of differences**

MI features	Under 40		Over 60			
	Per cent mean	S D	Mean	S D	t	P
History						
Angina pectoris	[illegible] 5	3 8	67 4	4 3	7 9	<0 001
Arterial hypertension	18 4	3 5	37 [illegible]	4 4	3 7	<0 001
Arrhythmias or conduction defects	5 8	2 1	21 6	3 7	3 7	<0 001
Circulatory insufficiency	3 4	1 6	[illegible]7 5	4 1	5 5	<0 001
Previous MI	9 [illegible]	2 7	25 0	4 5	3 3	<0 001
Symptoms and complications						
Precordial pain	82 5	3 5	53 5	4 6	5 1	<0 001
Cardiogenic shock	7 5	2 4	[illegible]8 3	4 1	4 4	<0 001
Circulatory insufficiency	9 [illegible]	2 6	57 5	4 5	9 2	<0 001
Ventricular aneurysm	22 5	3 8	[illegible]0 8	3 7	0 3	n s
Cardiac rupture	—	—	5 0	[illegible] 0	2 6	0 008
Arrhythmias and conduction defects	[illegible]3 3	3 8	6 [illegible]	4 4	8 8	<0 001
Thromboembolism	7 5	2 4	13 3	3 1	1 [illegible]	n s
Mortality rate	14 2	3 2	30 8	4 3	3 2	<0 00[illegible]

*C od sed f m G re h[9] tabl s 1 th ough 3

not a prerequisite for the diagnosis of a microinfarct as shown for instance in the illustration of one of the cases of Aronov [7] Trushinsky and associates[8] state that interpretation of micro MI was based mainly on clinical and laboratory data in presence of ischemic electrocardiographic changes Consequently many of the cases with micro MI would be classified in Western epidemiologic research as nonspecific ST T changes or coronary insufficiency The differentiation between severe coronary insufficiency (possibly corresponding to small foci of necrosis) and MI is admittedly arbitrary It is generally recognized that any non pecific electrocardiographic change will corroborate the clinical picture of acute MI and subendocardial or intramural MI do not necessarily produce abnormal Q waves (or absent R waves in precordial leads) Thus there is some justification in lumping together micro- and macro MI in the over all statistics of MI However this will increase the incidence of MI as compared to Western epidemiologic material Perhaps the Russian criteria for MI are more comparable to the more general classification ischemic heart disease However since the same criteria were applied to young and older patients the comparison of different age-dependent features of MI may be valid

Statistical analysis

While the number of Russian publications on MI in young people is large we found only two papers with statistical evaluation in the comparison of older and young patients with MI Gurevich[9] compared a sample of 120 patients (103 men 17 women) under 40 years and 120 patients (77 men 43 women) over 60 years Trushinsky and co workers[8] compared 79 patients 29 to 44 years 755 patients 45 to 64 years and 289 patients 65 to 86 years a total of 1 123 patients which is the largest sample with analyzed age differences

Table I shows a condensation of the results of Gurevich [9] and Table II a condensation of the results of Trushinsky and associates [8] The age distribution of Gurevich s two groups and of Trushinsky s three groups is overlapping which may explain in part some of the discrepancies According to Table II the decrease of the incidence of precordial pain and increase of arrhythmias occurs only in the oldest ag

*Table II Incidence (in per cent) of various features of MI in three age groups**

MI features	*A*	*B*	*C*	*P* *A B*	*P* *B C*
Previous MI	9.0	31.3	29.9	<0.001	n.s
Precordial pain	86.1	81.7	71.2	n.s	<0.001
Shock (severe)	6.3	11.0	11.7	<0.05	n.s
Cardiac decompensation	10.3	20.5	33.2	<0.001	<0.001
Thromboembolic complications	2.5	8.1	12.2	<0.001	<0.05
Ventricular aneurysm	1.3	7.8	14.2	<0.001	<0.001
Extrasystoles	5.3	9.7	17.3	n.s	<0.001
Other arrhythmias and conduction defects	9.0	10.7	16.3	n.s	<0.001
Mortality rate	5.1	13.0	29.1	<0.001	<0.001

Group A 7[illegible] patients from 29 to 44 years old B 755 patients from 45 to 64 years old C 289 patients from 65 to 86 years old
There was no significant difference between the three age groups in increase of temperature leukocytosis and sedimentation rate
n.s = not significant
*Condensed from Trushinsky and associates[8] tables 1 2 and 3 and Fig 3

group In contrast to the Trushinsky study, Gurevich found no statistically significant difference in thromboembolic complications and ventricular aneurysm, while the increase of temperature leukocytosis and transaminase was less pronounced in the older age group (not included in table) In all other respects, the results of the two studies agree fairly well (increased frequency of various complications and death in the older age group)

Incidence

The incidence of MI in patients under 40 years in percentage of a total MI population varies widely in various reports from 2.7 to 20 per cent, as reviewed by Gurevich[6] Romanov[5] surveyed a total of 15 666 cases of MI in the Russian and Western literature 4.95 per cent of the patients were below 40 years and only 0.42 per cent below 30 years of age This is quite similar to the incidence of 5.5 per cent of patients below 40 in Romanov's own material In Trushinsky's sample, the percentage of patients below 45 years was 7 per cent, but only 0.5 per cent in patients under 31 years Nedlina[4] reported 4.5 per cent of MI patients under 40 years out of a total of 471 cases nearly identical to the 4.97 per cent found by Sukhinin and Dvorina[10] In Shestakov's[11] study, the percentage was 12.5

Prior to World War II, coronary disease was uncommonly diagnosed before the fifth decade in men in the United States[12] Such occurrences appear in the medical literature as case reports[12] The largest series in young men is that of Yater and colleagues[12] reporting 866 men under age 40 selected from the United States Armed Forces in World War II[14] Enos and associates[14] report evidence of coronary disease in 77.3 per cent of 300 American battle casualties in the Korean War Their average age was 22.1

MI in children is rare, but two cases have been published by Krimskii and Arutionov[15] and one case by Sokolovskaya and Pavlova[16] The two patients of Krimskii and Arutionov were a boy of 4 years and a girl of 4½ years Both had Fallot s tetralogy In both cases, numerous foci of myocardial necrosis and sclerosis were found, but the coronary arteries were normal The 5 year old patient of Sokolovskaya and Pavlova[16] was under observation for congenital heart disease There was some history of angina pectoris with increased temperature After three months in the hospital an acute episode occurred with the typical symptoms of MI with cardiac decompensation Fig 1 shows the ECG before and during this episode Autopsy revealed biventricular hypertrophy subacute septic endocarditis involving the mitral and aortic valves and septic infarct of the left ventricle (upper posterior wall) and pericarditis In the pediatric age group arteriosclerosis of the coronary vessels is not uncommon as an incidental pathologic finding at autopsy but

clinical and fatal myocardial infarctions are usually due to an etiology other than arteriosclerosis [14]

All authors[2 4 8 10 15 19] agree that the male/female ratio is significantly greater in younger than in older patients The ratios found in patients under 40 years vary from 7 1 to 10 1 mostly about 4 5 1 In Trushinsky s three age groups the ratio was 6 1 in the 25 to 44 year old group 1 6 1 in the 45 to 64 year-old group and 0 96 1 in the 65 to 84 year-old group These results are in general agreement with Western epidemiologic studies Coronary disease, especially fatal coronary disease is a rarity in women under age 40 [20] and in the young woman the diagnosis of clinical myocardial infarction may be in error [21] The high ratio of males to females suffering from coronary disease is accentuated in the younger ages A Seattle study[20] showed deaths from coronary disease under age 50 are 11 1 male to female and all the female deaths occurred after age 40 It is of interest that in contrast to older patients there is no prevalence of young patients with sedentary occupation [18]

Etiology

In the majority of MI patients under 40 years the cause is early coronary atherosclerosis This conclusion is supported by autopsy data [1 2 15 22 2] Lober s[26] measurements of coronary arteries in 536 hearts of noncoronary patients give a background for these results degenerative changes (narrowing of lumen increasing outer diameter infiltration of intima etc) start as early as the second decade and are progressive with age It appears to be safe to assume that in a relatively small percentage (about 5 per cent) the atherosclerotic degeneration is accelerated possibly hereditary factors play a contributing role [27] Zhivoderov and Kuznetsova[19] found cardiovascular disease in 71 8 per cent of close relatives in their sample of 157 young patients with MI According to Smolyannikov [23] coronary atherosclerosis in young patients usually involves only one major branch (more frequently the left coronary artery) in contrast to older patients with involvement of several branches Even small changes of coronary arteries may produce a serious impediment of myocardial blood supply if

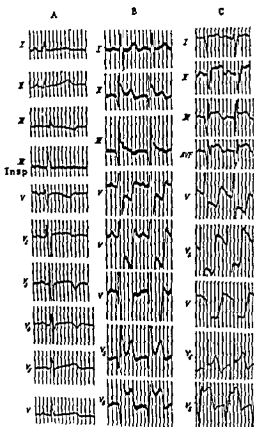


Fig 1 Myocardial infarction in a 5 year-old girl A IX/21 B XII/26 C XII/28 (From Sokolovskaya F Y and Pavlova Y P Pediatriia 5 85 1964 [Russ])

located in critical places of the arteries [8]

The majority of the patients below 40 years were between 30 and 40 years For patients under 30 years other types of etiology were more important but we were not able to find adequate autopsy material with statistical comparison of different types of etiology in age groups below 40 years We refer to the three cases of children between 4 and 5 years discussed earlier with MI on the basis of congenital heart disease

The second most frequent cause according to Soviet cardiologists is coronary endarteritis on the basis of rheumatic heart disease Other causes are coronary emboli in chronic septic endocarditis[4 8 15 17] and anomalies of the coronary arteries [28] In one of Gurevich s[1] patients the MI was due to syphilitic mesaortitis which obstructed the opening of the coronary arteries Thus in

contrast to the monoetiology of MI in older patients there appears to be a polyetiology in young patients [6,**]

Precipitating factors and history

Among precipitating factors, i.e., those immediately preceding the occurrence of MI, excessive physical effort (running, skiing, athletic games, lifting heavy loads, etc.) takes first place among young patients, more so than in older patients [1,3,6,7,18,19,9] This is probably due to the fact that young people are more likely to be engaged in heavy exertion than older people. Other contributing factors are alcohol intoxication, [11,18] excessive smoking [7] and emotional upset [2,4,10,18,19] Several authors found in the anamnesis blunt skull trauma [19,**] Moiseev and Borisenko[30] stress the significance of chest trauma, which results in subintimal hemorrhage. Arterial hypertension as a potential contributing factor is less important in younger than in older patients[5,10,2,31] (see also Table I)

In the majority of young patients there is usually no history of angina pectoris or other diseases which may be contributing factors to the development of MI (see Table I), i.e., the MI occurs when the patient is apparently in perfect health [4,6,18] Smolyannikov [3] found in 22 of 118 patients preinfarct symptoms (angina) 1 to 14 days before the acute episode. Silent MI is less frequent in younger than in older patients [**]

Clinical course

The clinical course would depend on the extent of the MI, development of the collateral circulation, and complications such as shock or arrhythmias. For a valid comparison of the clinical course between younger and older patients the samples should be matched as to the severity of the MI, as done in the extensive studies for evaluation of anticoagulant therapy. No such studies have been reported. However, it is recognized that such matching would tend to obscure some of the differences in the clinical course.

While the extent of the MI cannot be accurately estimated from electrocardiographic changes, it appears reasonably safe to assume that in comparison of samples "macro MI" represents a more extensive lesion than "micro MI" (see under Criterion). Micro MI is less frequent (about 10 per cent) in young patients [7,8,10] The large majority of patients show evidence of a major infarct, mostly localized in the anterior wall [7,10,18] The symptoms are quite typical, more so than in older patients. Crushing precordial pain is significantly more frequent (see Tables I and II). However, it is more promptly relieved by nitroglycerin or other coronary drugs than in older patients [2] Therefore, the recognition of MI in young patients is fairly easy [4,8] On the other hand, according to Lebedeva [14] diagnostic errors in the recognition of MI (such as gastric ulcer, food poisoning, or "ostrii zhivot"—i.e., acute abdomen) are not infrequent, leading to late hospitalization. The reason for late recognition or failure of recognition may be the fact that MI was not expected because of the young age of the patients.

Shock and cardiac decompensation are less frequent (Tables I and II and Gurevich[6,9]) and in contrast to older patients cerebral symptoms are practically absent [5,9,10,2,33] In contrast, Zhivoderov and Kuznetsova[19] report a rather high frequency of shock. It appears that in the majority of studies the incidence of shock and cardiac decompensation was less in younger than in older patients. Galenina and associates[34] suggest that the greater vasomotor reactivity in young patients plays an important role in the pathogenesis of shock (reflex collapse).

According to Korkushko[35] (quoted from Gurevich[6]) changes of cardiac output, stroke volume, peripheral resistance are less pronounced in young than in old MI patients. Sidorovich [2*] on the other hand found no age difference in contractility (systolic phases investigated by means of polygraphy) in 70 patients under 40 years and 107 patients over 40 years, although disturbance in contractility was observed in all patients. Similarly, ballistocardiography, x-ray kymography, and rheography did not reveal significant differences in the mechanics of systole [36,39]

Ventricular aneurysm

The experience of various authors about the frequency of aneurysm is not uniform. According to Trushinsky and associates[8] (Table II), there is a significant increase in

the frequency with age while Gurevich[9] (Table I) found no significant age difference The reported percentage of 22 5 (young patients) and 20 8 (older patients) is amazingly high far exceeding that in Trushinsky s oldest age group (65 to 84 years) The clinical diagnosis of ventricular aneurysm from x ray is often not easy although the error is more in line with false negative than with false positive diagnoses The electrocardiographic criteria (prolonged S T elevation) are also not reliable No criteria for the diagnoses of ventricular aneurysm were given in these two papers A rather high incidence of ventricular aneurysm was also found by Rom Bugoslavskay and Shub[40] and Lebedeva [18] Details of the x ray confirmation with criteria were given by Rom Bugoslavskay and Shub The incidence of 10 out of 26 patients with ventricular aneurysm in Lebedeva s[18] sample is quite extreme The discrepancies are probably due in part to differences in the criteria used but it appears ventricular aneurysm is not a rare complication of MI in the experience of Russian authors

Cardiac rupture was not seen in young MI patients while it occurred in 5 per cent of older patients (Table I)

There is a significant increase of various arrhythmias and conduction defects with age (Trushinsky and associates [5] table 2) Gurevich[6] states in his review that serious types of arrhythmias and conduction defects are rare in young MI patients but a reverse age difference is shown in his earlier analysis[9] (Table I) This is not necessarily a contradiction since in Table 1 probably all types of arrhythmias are lumped together

Blood coagulation The blood coagulation of young MI patients is within normal limits[32 11 41] in contrast to older MI patients Thromboembolic complications increased significantly with age in Trushinsky s extensive study (Table 2) According to Russian authors anticoagulation therapy is not indicated for the large majority of young MI patients

The information about fever leukocytosis and sedimentation rate is controversial An exaggerated reaction in young patients was noted by Gurevich [9] In Romanov s[4] sample of 47 young MI patients there was such wide variation of temperature increase from zero to fever for several weeks that any attempt to find significant differences between old and young MI patients would be quite meaningless Trushinsky and associates found an accelerated sedimentation rate and leukocytosis in a significantly smaller percentage of younger than of old MI patients Gurevich[9] reported a greater increase of transaminase in young MI patients

Experimental coronary occlusion In view of the controversial information about some characteristics of MI in young patients Kostiuk s[43] experiments on the effect of coronary occlusion in 27 young (1 to 2 years) and 30 old (over 4 years) rabbits are of interest Irreversible ventricular fibrillation occurred in 4 young and in 11 old animals In the old animals ventricular fibrillation produced cardiac arrest much faster than in the young animals The author suggested that coronary occlusion produced a more acute and more pronounced myocardial hypoxia in the old animals In some of the older animals late S T changes developed after the initial S T elevation had subsided (i e 3 days after occlusion) There was also a different reaction of the systolic blood pressure as shown in Fig 2 The initial drop after occlusion was more pronounced in young animals but it recovered faster exceeding the initial (preinfarct) level within one to two days rarely after 3 days In older animals the initial level was attained only from 7 to 20 days after occlusion The majority of young animals responded to occlusion with increase of heart rate while the reaction of the older animals was not uniform Simulated high altitude (3 000 to 7 000 M) produced greater reaction of blood pressure and ECG (S T depression) in the old animals Pituitrin injection two days after occlusion produced bradycardia and no or only short (1 to 2 minute) arrhythmias in the young animals while in the older animals bradycardia was associated with long periods (15 to 20 minutes) of heterotopic arrhythmias S T depression was more pronounced and prolonged in the older animals The orthostatic test applied 1 to 3 days after occlusion produced in the older animals bradycardia and quite often heterotopic arrhythmias while the young animals responded with tachycardia While

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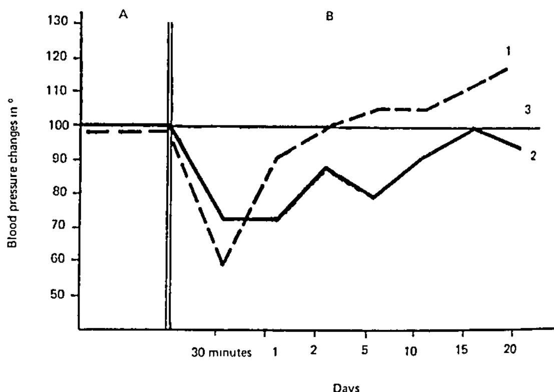


Fig 2 Changes of systolic arterial blood pressure in per cent of initial value (*100*) before (*A*) and after (*B*) coronary occlusion of a young (*1*) and old (*2*) rabbit *3* Base line (From Kostiuk I V *Vestn AMN SSSR Akad Med Nauk 18* 77 1963 [Russ])

it is questionable how far the results are applicable to men they show different cardiovascular reflex reaction in the two age groups together with more pronounced disturbance in the old animals

According to Tables I and II, the clinical course is relatively light and uncomplicated in the majority of young MI patients The experience of the different authors however, is not uniform Lebedeva[18] found a grave clinical course in the majority of patients

Mortality rate

There are obviously factors which tend to affect the course in different directions mitigating—the smaller incidence of shock cardiac decompensation arrhythmias, and absence of previous MI aggravating—the larger extent of the MI in the majority of young MI patients, and poor development of collateral circulation (Gurevich[8]) This is reflected in the mortality rate which varies from 5 1 to 20 per cent (Table III) While the mortality rate of older MI patients is greater, in most of the investigations it is still quite high in young MI patients

There is however, agreement that after the critical acute period the recovery is fast and more complete and rehabilitation prospects are favorable in young MI patients[2 6 39]

For comparison a few mortality data from studies in the United States are of interest Roth and co workers[44] found the hospital mortality rate in patients under 40 to be 2 per cent compared to over 30 per cent over 40 years of age They note an absence of Negroes in their group drawn from a population of 15 per cent Negroes suggesting a racial factor However, the total number of 53 is too small for significance Although myocardial infarction is considered to have a more favorable outcome in younger age groups Zukel and colleagues[45] showed a higher first year mortality rate for the age group 20 to 29 There after survival favored the younger men who had a better chance for 10 year survival (60 per cent) than the survival rate of all age groups (15 9 per cent) Beard and associates[46] showed a direct relationship between age and immediate death varying from 10 per cent under age 40 to 30 per cent at age 70 or over

Table III Mortality rate of young MI patients

Sample size	Per cent	Author
58	14 0	Sukhinin and Dvorina[9]
120	14 2	Gurevich[6]
90	17 8	Klimenko[3]
80	20 0	Klimenko and Lyba[2]
79	5 1	Trushinsky et al[8]
47	19 2	Romanov

Summary

The high incidence of myocardial infarction in young people has been of major concern to Russian cardiologists resulting in a large number of publications in the past 15 years This is a review of the most important Russian publications in regard to the differences in the clinical course symptoms complications precipitating factors etiology and mortality rate in young and old patients with myocardial infarctions

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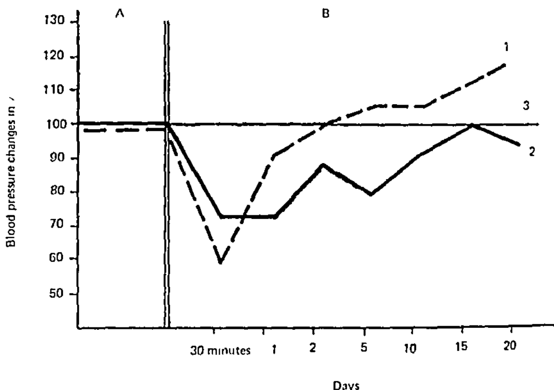


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Mortality rate

There are obviously factors which tend to affect the course in different directions: mitigating—the smaller incidence of shock, cardiac decompensation, arrhythmias, and absence of previous MI; aggravating—the larger extent of the MI in the majority of young MI patients and poor development of collateral circulation (Gurevich[6]). This is reflected in the mortality rate which varies from 5.1 to 20 per cent (Table III). While the mortality rate of older MI patients is greater, in most of the investigations it is still quite high in young MI patients.

There is, however, agreement that after the critical acute period the recovery is fast and more complete and rehabilitation prospects are favorable in young MI patients.[2,6,39]

For comparison, a few mortality data from studies in the United States are of interest. Roth and co-workers[44] found the hospital mortality rate in patients under 40 to be 2 per cent compared to over 30 per cent over 40 years of age. They note an absence of Negroes in their group drawn from a population of 15 per cent Negroes, suggesting a racial factor. However, the total number of 53 is too small for significance. Although myocardial infarction is considered to have a more favorable outcome in younger age groups, Zukel and colleagues[45] showed a higher first year mortality rate for the age group 20 to 29. Thereafter, survival favored the younger men who had a better chance for 10 year survival (60 per cent) than the survival rate of all age groups (15.9 per cent). Beard and associates[46] showed a direct relationship between age and immediate death varying from 10 per cent under age 40 to 30 per cent at age 70 or over.

virus in 1962[16,17] led to the use of virus isolation techniques and antibody determinations to confirm that the defects in the newborn infant were the result of intrauterine infection with those particular viruses The epidemiologic and laboratory data available to date on each of the viral agents which are known or believed to be likely etiologic agents in congenital heart disease are summarized below

Rubella It has been conclusively proved that rubella virus is etiologically related to congenital heart disease The large rubella epidemic in the United States in 1964 provided an opportunity for further confirmation of Gregg s earlier observations[18] This association was documented not only by the occurrence of clinical rubella in the woman with early gestation but more importantly by virus isolation and/or the demonstration of a significant rise (fourfold or greater) in rubella antibody titer during the course of the pregnancy Virus was also isolated from fetal tissues obtained following abortion or stillbirth from the newborn infant immediately after birth and from the throat and other sites of involved infants for many months after birth Specific anti rubella antibodies are produced by the congenitally infected fetus and infant IgM antibodies which are not passed transplacentally from the mother to the fetus are present in umbilical cord blood or in blood obtained from the newborn infant shortly after birth IgG antibodies produced by the infant are demonstrable in the serum over 6 months of age a time after which maternal transplacentally transmitted IgG would no longer be present[18]

The clinical manifestations of the congenital rubella syndrome are well described and include low birth weight due to intrauterine growth retardation cardiac malformations cataracts and microphthalmia mental retardation hepatosplenomegaly thrombocytopenic purpura and lesions in the long bones[5] The incidence of congenitally acquired rubella is approximately 1 case per 1 000 live births during nonepidemic periods (pre rubella vaccine data) but rose to 7 cases per 1 000 births during the 1964 epidemic The frequency of all malformations is highest when the maternal infection occurs early in pregnancy—a 10 to 50 per cent malformation rate with infection in the first month a 14 to 25 per cent malformation rate in the second month and a 7 to 17 per cent malformation rate in the third month[6] Congenital heart disease occurred in 48 per cent of a series of 376 children with rubella syndrome[19] The most common cardiac lesions in 87 catheterized patients were patent ductus arteriosus in 78 per cent right pulmonary artery stenosis in 70 per cent left pulmonary artery stenosis in 56 per cent valvular pulmonic stenosis in 40 per cent mild aortic valvular stenosis in 14 per cent aberrant subclavian artery in 11 per cent and ventricular septal defect in 10 per cent It is clear that the majority of cardiac malformations occur when rubella infects the mother during the first trimester although pulmonary artery stenosis has been reported following rubella infection after the first trimester[20] It has been estimated that maternal rubella may account for between 1 and 2 per cent of all malformations of the heart[1]

Rubella is the only viral agent which has been proved to be a true teratogen that is which results in congenital *malformations* Hence knowledge of the mechanisms by which rubella causes deformities may lead to a more basic understanding of the pathogenesis of congenital malformation of the heart Rubella is a noncytolytic virus in certain tissues that is it does not destroy the cells in which it replicates This characteristic would tend to allow survival of the infected fetus yet result in disordered function of cells tissues and organs On the other hand selective cell destruction may occur In pathologic studies of therapeutically aborted rubella infected fetuses scattered foci of necrotic cellular damage without inflammatory infiltrate were noted in endothelial cells of blood vessels and in myocardial cells[8] These rubella induced defects could result in the defective form and/or function of the developing tissue by direct cellular destruction or hypoxic damage secondary to blood vessel obliteration Alteration of the elastic or muscle fibers in the ductus arteriosus for example could be the reason for the failure of postnatal ductus closure Studies with tissue obtained from infants with rubella syndrome and maintained in culture revealed that the cells were persistently infected with rubella

Viruses as etiologic agents

There are five reasons why viruses have been considered likely causative agents in the genesis of congenital heart disease. First, there is the firmly established precedent of intrauterine infection with rubella virus during the first trimester of pregnancy leading to multiple congenital anomalies including those of the heart. Second, viruses are ubiquitous. Approximately 5 per cent of pregnancies have been shown to be complicated by at least one definite or presumed virus infection exclusive of the common cold.[5] Most women might be expected to have at least one viral upper respiratory or gastrointestinal tract infection during any 9 month period. Third, the majority of virus infections in the adult are subclinical, or produce only minimal disease. Thus a virus infection could be unrecognized in the mother, yet produce significant disease in the fetus. This situation, then, could lead to the occurrence of a "congenital defect of unknown etiology." Fourth, viruses are known to multiply readily in rapidly dividing immature cells with resultant cell destruction or alteration of cell function.[6] With more destructive viruses (e.g., measles or vaccinia) fetal death with abortion or stillbirth can occur. With less destructive agents (e.g., rubella or cytomegalovirus) the fetus may survive but defects are present at birth. Fifth, there are numerous examples in experimental animals where infection with a virus results in little or no disease in the pregnant mother, yet the fetuses are aborted or the newborn offspring are deformed.[7]

Maternal viral infections that do not have significant viremia as part of their pathogenesis are unlikely to pose a threat to the fetus. Although fetal death and abortion or stillbirth have resulted from indirect or toxic effects of virus infection (through disease in the mother or alteration of placental function), clinical and experimental data suggest that direct fetal infection is necessary for congenital defects to occur.[5,6] The placenta acts as an effective barrier against most viral agents that gain access to the maternal circulation. Certain viruses, however, can infect susceptible cells of the placenta and reach the fetal circulation by growth through the layers of the placenta rather than by passive diffusion. Alternate mechanisms of fetal infection could be virus induced vascular lesions in the placenta which result in abnormal communication between maternal and fetal circulations,[8] or diapedesis of maternal virus infected leukocytes through the placental layers to the fetal circulation.[9-11]

In general, two different epidemiologic methods have been utilized to explore the viral etiology of congenital malformations: retrospective analysis and prospective studies.[12] The former technique was utilized by Gregg[13] in making the association between the increased incidence of congenital cataracts and a prior rubella epidemic in Australia. The accuracy of this method depends on several factors: (1) a viral illness in pregnant women which is clinically manifest to a degree sufficient to allow a definitive etiologic diagnosis to be made in the majority of individuals infected, (2) an accurate memory on the part of the mother or a visit to a physician during the illness so that the disease is recorded, or (3) the occurrence of an epidemic due to a particular agent which is recognized by the health authorities and which, if it produces disease in the fetus, presents a uniform clinical pattern. Prospective studies are more difficult and costly to perform for several reasons: (1) because large numbers of pregnancies must be involved in order to provide a sufficient number of anomalies for statistical evaluation, (2) because the majority of virus infections during pregnancy are subclinical, acute and convalescent serum samples from the mother must be available for serologic survey of a number of viruses, (3) because the critical time for the occurrence of fetal deformities is the first trimester, ideally the mother should be enrolled in the study early in gestation so that any serum samples obtained would bracket a subsequent viral illness.

Although prospective studies are more involved than retrospective analyses, both epidemiologic approaches have nevertheless provided considerable useful information and have frequently suggested leads for further study. Important verification of the association of a given virus with a particular constellation of congenital defects has also been provided by the laboratory. The successful propagation in tissue culture of cytomegalovirus in 1956[14] and of rubella

B viruses which was associated with an increased incidence of congenital heart disease[32] An animal model for Coxsackie B virus infection and congenital heart disease has not been developed The virus is transmitted transplacentally in the mouse fetal infection and death results but no anomaly[33] The evidence then for Coxsackie B virus etiology of congenital heart lesions is strongly suggestive but not yet positive

Additional information or studies which would provide further evidence for the association include (1) confirmation by other laboratories of the provocative serologic studies of Brown and Evans[27] (2) the demonstration of specific IgM antibodies in umbilical cord or neonatal sera directed against the Coxsackie B viruses in significant numbers of infants with congenital heart lesions as compared with control infants (3) the isolation of Coxsackie B viruses from significant numbers of newborn infants with congenital heart disease as compared with the isolation from normal control infants and (4) the identification of Coxsackie B virus antigen in the myocardium and/or cardiac lesions of a significant number of infants who died with congenital heart disease as compared with infants who died from noncardiac and noninfectious causes

Mumps The issue of the relationship between intrauterine mumps virus infection and postnatal endocardial fibroelastosis (EFE) remains controversial[34, 35] The clinical evidence supporting this relationship is the occurrence of a significantly higher incidence of skin test positivity to mumps antigen in patients with EFE than in matched controls However mumps virus has not been isolated from these patients and mumps antibody has usually not been present in their serum For the newborn infant to have a positive skin test without the presence of virus or antibody the fetus must (1) recover from the virus infection *in utero* so that the virus cannot be isolated after birth and (2) manifest a cellular but not humoral immune response against the mumps virus antigen so that delayed hypersensitivity but not antibody is demonstrable It is appropriate to examine the available experimental data concerning the fetal response in order to determine the validity of these hypotheses

Fetal recovery from intrauterine virus infection has been documented and transplacental passage of maternal antibody may play a role in this recovery process[6] Development of a cellular immune response without a humoral immune response in the fetus could occur by one of several mechanisms (1) a tolerance could develop with respect to humoral but not cellular immunity (2) the virus infection could occur at such a time during the ontogeny of the immune response in the fetus that the capacity to express cellular immunity was present but not the ability to produce antibody and (3) maternal passive antibody could inhibit humoral but not cellular immunity Most experimental evidence would argue against the first two mechanisms In the animal models where antibody tolerance to intrauterine virus infection exists there has been demonstrable persistence of virus in the circulating blood and tissues[6, 24] As noted mumps virus has not been isolated from patients with EFE In most mammalian species where the ontogeny of the immune response has been examined the capacity to produce antibody develops prior to the ability to reject skin grafts or to manifest skin test-delayed hypersensitivity[36] The postulated mumps–EFE association requires that delayed hypersensitivity develop prior to antibody production The inhibition of antibody production by passive antibody administration has been shown to occur[26] this mechanism therefore remains a possibility

There are additional difficulties in the attempts to associate intrauterine mumps with EFE The accuracy of the mumps skin test (on which the relationship with EFE rests) in predicting individuals with prior exposure to mumps virus has been questioned[37] Of particular importance is the fact that individuals with positive skin tests have contracted mumps indicating that false positive tests can occur In addition children with EFE have contracted mumps[35] In the consideration of maternal gestational mumps the available clinical information does not support the mumps EFE relationship Although some prospective studies have shown an increased incidence of abortion and stillbirth following gestational mumps most have not demonstrated an increase in congenital malforma

virus and had a decreased growth rate and shortened survival time.[1] Naeye and Blanc[2] noted that the growth retardation in infants with the rubella syndrome was the result of a decreased number of cells in the organs. This impaired cellular growth, if it occurred during a crucial phase in cardiac development, could well result in such cardiac anomalies as septal defects. Increased numbers of chromosome breaks have been noted in leukocyte cultures of children with congenital rubella.[3] It is possible that this chromosomal injury results in cell loss (due to impaired DNA replication) during rapid organ development and is in part responsible for the congenital anomalies.

Transplacental infection with rubella virus has been demonstrated in the monkey, ferret, rabbit, and rat.[7] However, the complete rubella syndrome as it occurs in humans, particularly with regard to cardiac defects, has not been duplicated in experimental animals.[7,24] The neonatal rat is the only animal that has shown evidence of cardiac damage following gestational rubella.[5] Pathologic sections of the involved hearts revealed disrupted cords of cardiac muscle and septa, with scattered eosinophilic areas replacing cardiac tissue. Rubella virus antigen was demonstrated by immunofluorescence techniques in these same areas. There was no mention of gross cardiovascular defects.

There are many unanswered questions concerning the pathogenesis of congenital rubella. Why does the virus damage cells of the myocardium, lens, and inner ear in the fetus but not in the adult? Are similar pathogenic mechanisms instrumental in the production of cardiovascular anomalies and in producing damage to the lens? Is the disturbance in organogenesis primarily a matter of cell death or are more subtle derangements in cell function operative? The answers to these questions depend upon an increased understanding of the molecular biology of virus-cell interaction obtained through *in vitro* studies of human tissue and the use of animal models.

Coxsackie B virus. There is strong circumstantial evidence that the Coxsackie B group of viruses may be etiologically associated with congenital heart disease. These viruses are the most common agents known to cause myocarditis and pericarditis in children and adults, thus demonstrating their strong cardiotropic potential.[26] Transplacental infection of the late gestation fetus has been reported with disseminated disease presenting in the newborn infant as myocarditis, hepatitis, and meningoencephalitis.[6] Brown and Evans,[27] in a prospective study, demonstrated the significant association between serologic evidence of Coxsackie B3 and B4 virus infection in mothers during the first trimester of pregnancy and the birth of infants with various types of congenital heart disease. Approximately half of the maternal infections were completely subclinical; in those cases where symptoms occurred, none would have permitted a specific clinical diagnosis. There was no difference between mothers of infants with congenital abnormalities and matched control mothers of normal infants with regard to the incidence of infection with other Coxsackie virus types B1, B2, B5, and A9, with ECHO virus types 6 and 9, with influenza virus types A and B, or with the adenovirus group. There was no serologic evidence of rubella in any of the mothers who gave birth to infants with heart anomalies. Virus isolation and antibody studies were not done on the infants. Burch and co-workers[28] demonstrated the presence of Coxsackie B virus antigen by immunofluorescence techniques in myocardial tissue obtained at routine autopsies from infants and children. Twenty-nine of 50 hearts examined showed interstitial myocarditis; in 12 of these specific antigen was demonstrated. Five infants in this latter group either were stillborn or died within hours after birth, further documenting the transplacental passage of this group of agents. None of these five infants, however, had evidence of congenital heart disease. In a previous publication by this same group of investigators,[29] Coxsackie B antigen was demonstrated in the myocardium of an infant who died at 2 days of age and who had a widely patent ductus arteriosus. Bates[30] described a stillborn infant with calcific pancarditis and hydrops fetalis in whose myocardium specific Coxsackie B3 virus antigen was demonstrated. No gross cardiovascular anomaly was noted. In contrast to rubella, no large-scale epidemic has been reported with Coxsackie

cause congenital heart disease is long It is not possible to predict which viruses are likely to cause fetal abnormalities from the diseases that these viruses produce in children and adults Fifty years ago who would have predicted that rubella or cytomegalovirus infections would be significant factors in the genesis of congenital defects? It becomes obvious then that the task of identifying specific viruses as etiologic agents in the entire spectrum of congenital heart disease will not be an easy one

Future efforts

The areas of research which would appear to hold the greatest promise for future investigation fall into one of four categories (1) the epidemiology of congenital heart disease (2) the association of maternal viral infection with abnormal offspring (3) the in-depth virologic investigation of the infant with a cardiac defect and (4) the development of experimental animal models of congenital heart disease

More precise epidemiologic surveillance data are needed to determine two aspects of congenital heart disease (1) the frequency of occurrence of the various types of defects in different populations and (2) the effect of race geography climate or season of the year on the occurrence of these defects The correlation between recognized patterns of epidemiology and the pathogenesis of infectious diseases and the occurrence of congenital heart disease will provide leads for the possible association of particular viral agents with specific heart lesions and will suggest areas for further in depth study For example an association has been reported between seasons of the year and the birth of children with patent ductus arteriosus [1] A search for possible causative viruses by both epidemiologic and laboratory means could focus initially on those agents known to be seasonally prevalent at the time of or shortly after conception in these pregnancies Other epidemiologic factors such as (1) the frequency of infection in women of childbearing age with the suspected viruses and (2) the occurrence of viremia as part of the pathogenesis of the disease in the mother can be utilized to narrow the spectrum of viral agents even further

In the consideration of future efforts to associate specific viral agents with particular constellations of congenital defects it is appropriate to examine the approaches utilized in the establishment of rubella and cytomegalovirus as causative agents of congenital abnormalities Although the documentation of maternal infection during pregnancy and the association with abnormal offspring will provide important suggestive information proof of the association must come from evidence of infection in the abnormal newborn With all the negative data from previous reports it is unlikely that clinically recognized viral infections during pregnancy are a major cause of congenital malformations Thus for the reasons noted above the most productive information concerning maternal infection will likely come from large prospective studies

Extensive virus isolation and serologic studies should be attempted in defective neonates where the etiology is not readily apparent In congenital rubella and cytomegalovirus infections and in virtually all of the animal models of intrauterine virus infections either virus or antibody or both are demonstrable in the newborn By focusing on the abnormal newborn the investigator can be more selective in terms of numbers of patients and he can proceed with more in-depth studies One can question however whether the absence of a demonstrable viral agent or of a specific antibody in the newborn infant can in fact rule out an intrauterine virus infection The obvious exception would be when the infection is due to a new viral agent which had not previously been isolated or to a known agent which would not grow in the cell culture systems routinely utilized for virus isolation The approach to this problem would of course be the application of the new not previously utilized techniques available for culturing and identifying viral agents The success of this approach requires that there be a persistent infection in the fetus so that the virus is present in the excretions or tissues of the newborn infant and/or that a fetal humoral immune response occur which results in antibody being present in the neonate

It is theoretically possible however that intrauterine virus infection could occur but that neither virus nor antibody would

tions[2,3,35] In the few case reports reviewed by Hyatt[39] of congenital abnormalities in infants whose mothers had mumps during pregnancy, a variety of types of defects occurred Cardiac lesions were infrequent and EFE was not specifically mentioned There has been little or no evidence that mumps infection occurred during pregnancy in the mothers of infants who developed EFE[35]

However, in support of the mumps virus etiology of EFE, there has been one case report[40] of acquired myocarditis and autopsy proved endocardial fibroelastosis following mumps virus infection in a 19 month old child In addition, there are experimental animal data to add to the evidence Infection of chick embryos with mumps virus during the very early phases of differentiation resulted in persistent virus infection, particularly of the heart and brain, and pathologic evidence of interstitial myocarditis in the late gestation embryo[41] Chicks at one year of age showed evidence of EFE Antibody was demonstrated by one month of age in the chicks but delayed hypersensitivity to mumps virus could not be elicited Direct inoculation of first trimester fetal monkeys with mumps virus resulted in virus replication which was controlled and led to the development of cellular immunity but no detectable humoral immunity in the newborn animals[4] To date, cardiac pathology has not been seen in the infected monkeys Thus, the chick embryo model provides evidence that gestational mumps can cause EFE and the monkey fetus model suggests that intrauterine mumps can result in cellular but not humoral immunity in the newborn

It would appear that there is suggestive evidence that gestational mumps is etiologically related to EFE however as noted there is conflicting evidence Further studies will be required before the relationship is conclusively proved or disproved Additional information which would be helpful in establishing the association includes (1) prospectively obtained virologic (virus isolation) or serologic (antibody titer rise) data that maternal mumps is associated with the birth of offspring who develop EFE, (2) the demonstration of mumps virus antigen in the myocardium or endocardium of patients with EFE and not in the heart tissue of patients the same age who died from noncardiac causes and (3) the demonstration that EFE can result in monkeys and other mammalian fetuses from the infection with mumps virus

Other viruses The only viral agents which have been conclusively proved to cause congenital defects are rubella and cytomegalovirus Cardiovascular anomalies however are infrequent findings in infants with congenital cytomegalovirus infection[5,42] It is not known whether the cardiac defects are a coincidental occurrence or the direct result of the intrauterine virus infection Influenza viruses and recently herpes simplex virus, have been incriminated by some studies as causing congenital defects but the abnormalities reported have usually been of the central nervous system[2,3,5,12] ECHO viruses might be considered likely candidates because infections are prevalent and frequently subclinical However several documented ECHO virus epidemics have not resulted in an increased incidence of abnormal offspring[2,12] Rhinoviruses the most frequent causative agents of the common cold, usually result in infections limited to the respiratory tract and would not be expected to cause fetal infection The recently isolated (by means of tracheal organ culture techniques) and described human coronaviruses also appear to cause mild or asymptomatic infections limited to the respiratory tract[44] These new organ culture techniques (e g , human fetal gut organ culture[4]), may result in the isolation and characterization of new viral agents associated with human disease which could have a role in the production of congenital malformations Infections with reoviruses are relatively common and usually asymptomatic but may have an associated viremia[46] Although reovirus type 1 has been shown to cause transplacental infection and abnormal offspring in mice[47] to the writer s knowledge the role of this group of agents in human intrauterine virus infection has not been examined The viruses which are known to cause transplacental infection and congenital defects in experimental animals[7] have been considered as possible agents in humans but their precise role has not been defined[48] It is apparent that the list of viral agents which could

following intravenous inoculation of the pregnant female with H 1 virus[51] The ideal natural virus model infection would be one in which the virus infected the mother causing little or no disease was passed transplacentally and resulted in infection of the fetus with the production of defects

Much of the work on fetal infection to date has been of a descriptive nature—i e which viruses can infect and cross the placenta which viruses infect and damage the fetus the time during gestation that maternal infection occurs which then results in fetal infection and disease and the pathologic nature of the fetal disease Much remains to be learned about the mechanisms of resistance to virus infection in the fetus and how these mechanisms differ from similar mechanisms in the adult We need to learn the basis for the enhanced susceptibility of the fetus to virus infection and what the role of the placenta is not only in preventing or in permitting transmission of virus to the fetus but also in assisting recovery from infection once the virus has reached the fetus

Prospects for control

The likelihood of developing effective means of preventing virus induced congenital heart disease in humans will depend on the results of the studies on etiology and on the pathogenesis of infections in the fetus If only a few viruses are identified as causative agents then the production of vaccines for immunization would be a feasible goal The development of rubella vaccine is a good example of successful efforts in this area However the mere identification of a teratogenic agent does not mean that successful vaccine production will ensue For example the prospects for a cytomegalovirus vaccine do not appear bright If the number of causative agents is large vaccine production would not be a practical solution and antiviral chemotherapy would provide an alternate approach Rapid and efficient means would have to be developed to provide an accurate etiologic diagnosis of virus infections during the early gestational period in the woman Once infection with a teratogenic agent was identified safe and effective antiviral drugs would be needed for treatment of the infection in the mother and in the fetus A great deal of work has been done and is currently in progress on the use of interferon[52] and interferon inducers[53] in the treatment of human viral disease Certainly further work is necessary to check the efficacy of these substances in experimental animals with a number of different types of virus infections before their use in human viral disease can be expected However limited clinical trials have been cautiously undertaken As will be obvious both the vaccine and the antiviral chemotherapeutic approach to the prevention and/or control of congenital heart disease is still a dream of the future It is only through the persistent and combined efforts of both clinical and laboratory research that sufficient information will become available to allow attempts to be made toward practical solutions of the problem

Summary

The etiologic basis for the vast majority of cases of congenital heart disease remains largely undefined Viruses have been considered to be likely candidates since the recognition of the association between intrauterine rubella and congenital heart disease Although the pathogenesis of cardiovascular defects is poorly understood information gained from the study of congenital rubella syndrome suggests that mechanisms such as focal endothelial cell damage resulting in obliteration of vascular supply decreased growth rate and shortened survival time of certain cells and disturbed DNA replication in cells whose chromosomes were damaged secondary to the effects of virus replication may be operative in the production of defects in the developing fetus In addition to rubella there is suggestive but not conclusive evidence that Coxsackie B3 and B4 virus infections during pregnancy can result in the birth of infants with a variety of types of congenital heart lesions and that intrauterine mumps virus infection may be etiologically related to the postnatal development of endocardial fibroelastosis (EFE) Although there are a number of other viruses that are potential etiologic agents of congenital heart disease the current status of information is inadequate to allow even suggestive associations to be made The most profitable areas for future inves

be demonstrable in the newborn infant even if techniques appropriate for that virus were utilized. The experimental data which would support or refute this hypothesis should be examined. A virus could infect the early gestation fetus and result in tissue destruction and/or alteration of organogenesis, yet be eliminated prior to birth. Recovery of the fetus from the infection could occur through the production and action of interferon, of maternal transplacental antibody, or through other nonspecific factors developed by the mother or through processes occurring in her, in the placenta, or in the fetus.[6,49] There are good clinical and experimental data to indicate that the fetus may be capable of controlling certain virus infections *in utero*, but the mechanisms responsible are poorly understood.[6,20,4,49] Absence of antibody in the newborn infant, even though there had been exposure to an antigen (virus) *in utero*, was shown to be possible in the discussion of the mumps–EFE hypothesis. Studies in the fetal lamb have shown that challenge of the immunologically immature fetus with an antigen will not elicit a detectable antibody response.[36,45] Challenge of that same fetus with the same antigen at a later gestational age or after birth at a time when it has developed the capacity to respond immunologically, results in a primary antibody response identical to that which would be expected if the animal had never been exposed to the antigen. In other words, there was no detectable primary antibody response to the antigen in the early gestation fetus, there was no evidence of a secondary or anamnestic response when the fetus was rechallenged with the same antigen, and there was no evidence of immunologic tolerance to the antigen. Each of these three parameters has been utilized to determine prior exposure to an antigen yet, as noted, none may be present in the newborn animal which received an antigenic challenge early in gestation.

Further work needs to be done to determine if virus infection of the early gestation fetus can result in a similar situation—recovery from the infection but no humoral evidence of contact with the virus antigen. The studies of St. Geme and associates[41,42] with mumps virus infection of the fetal monkey are important in this regard. Newborn monkeys were shown to have recovered from the virus infection *in utero* in the absence of detectable mumps antibody. Administration of mumps virus postnatally to the monkeys infected *in utero* elicited a normal primary antibody response.[50] These studies need to be extended to other viral agents suspected of causing congenital defects in humans. The use of animal models other than primates has been and should still be considered, since this species is expensive and technically difficult to work with.

If neither virus isolation nor antibody demonstration is possible in the newborn infant who had an intrauterine infection, then other means will have to be utilized. Frequently, viral antigen can be demonstrated in tissues by fluorescent antibody techniques when infectious virus cannot be recovered from the same tissues. The important observations of Burch and co-workers[23,9] concerning Coxsackie B virus antigen in myocardial tissues should be extended to other viruses. Tissue obtained at the time of cardiac surgery, as well as from autopsy material, could be utilized for these studies. It will be important, however, to demonstrate that this is a reliable technique for the association of specific viral agents with congenital heart lesions. For example, rubella virus antigen should be demonstrable in excised ductus tissue in infants with culture proved congenital rubella syndrome who are undergoing ligation of the ductus.

The use of experimental animals will provide the opportunity to determine if viral agents suspected of causing abnormalities in humans can produce defects in animals. In addition, if congenital defects produced in animal models are similar to those found in humans, this would permit the elucidation of mechanisms responsible for the genesis of these defects. Studies should be performed not only with human viruses but also with viral agents which are natural to that particular animal species.

To the writer's knowledge, a good mammalian animal model for congenital heart disease is not available. The microscopic lesions noted in the cardiac muscle of fetal rats infected with rubella virus were mentioned above.[25] Ectopic hearts were occasionally noted in hamster embryos infected

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tigation appear to be (1) the epidemiology of congenital heart disease, (2) prospective studies of the association of maternal viral infection with abnormal offspring (3) the in depth virologic investigation of the infant with a cardiac defect, and (4) the development of experimental animal models of congenital heart disease Successful control of virus induced congenital heart disease will depend on the results of these investigations and the development of vaccines against the identified causative viruses and/or safe and effective antiviral chemotherapy for the woman in early gestation who is infected with a known teratogenic agent

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week for eight patients on placebo or 6 3 anginal episodes per week per patient on placebo A mean difference of 1 3 anginal episodes per week in these eight patients is not clinically significant One also finds by analyzing his data that the mean nitroglycerin consumption per patient per week was 2 1 nitroglycerin tablets on alprenolol and 3 3 nitroglycerin tablets on placebo This difference in nitroglycerin consumption is also not clinically significant

In a later study Bjorntorp[6] found that the dextro isomer of alprenolol was ineffective as an antianginal drug However he[6] reported that the racemate of alprenolol administered to 11 patients with angina pectoris due to coronary artery disease in a dose of 400 mg daily significantly reduced the incidence of anginal episodes compared to placebo in a double blind study If one analyzes his data one finds that the mean incidence of anginal episodes was 7 9 anginal attacks per week per patient on placebo and 5 2 anginal episodes per week per patient on the racemate of alprenolol This difference in incidence of anginal attacks on the racemate of alprenolol compared to placebo is not clinically significant

Arstila and his associates found in a double blind study involving 28 patients with angina pectoris due to coronary artery disease who received 225 mg of alprenolol daily and placebo that alprenolol did not significantly reduce the incidence of anginal attacks in comparison with placebo These investigators also reported that nitroglycerin consumption was significantly smaller in patients taking alprenolol than in patients taking placebo during the second 4 week period but not during the third or fourth 4 week periods

Sowton and Smithen[8] reported in a double-blind crossover trial involving 17 patients with angina pectoris due to coronary artery disease that alprenolol administered in doses of 200 mg daily 400 mg daily and 800 mg daily did not cause any significant reduction in consumption of nitroglycerin tablets in comparison with placebo There was also no significant difference in the patients preference for alprenolol 200 mg daily alprenolol 400 mg daily alprenolol 800 mg daily or placebo These investigators did find a significant increase in exercise tolerance in the patients while taking alprenolol 200 mg daily and 400 mg daily but not while taking alprenolol 800 mg daily in comparison with placebo The mean increase in exercise performance in excess of that during the placebo period was 21 per cent while taking 200 mg daily of alprenolol and 17 per cent while taking 400 mg daily of alprenolol Sowton and Smithen[8] also stated that alprenolol 200 mg daily and 800 mg daily but not 400 mg daily significantly reduced the mean amount of ischemic ST segment depression at the onset of angina The mean amount of ischemic ST segment depression at the onset of angina was 1 1 mm on 200 mg of alprenolol daily compared to 1 4 mm on placebo and 0 7 mm on 800 mg of alprenolol daily compared to 1 1 mm on placebo

Pitt and Anderson[9] reported in a double blind study involving six patients with angina pectoris due to coronary artery disease that oxprenolol 120 mg daily proved useful in treating angina pectoris One of these six patients withdrew from their study because he developed a myocardial infarction while he was taking oxprenolol If one analyzes the data of the other five patients one finds that the average number of anginal episodes per week per patient was 4 3 anginal attacks on oxprenolol and 5 9 anginal episodes on placebo This difference is not clinically significant Further analysis of their data reveals that the average number of nitroglycerin tablets consumed per week per patient was 4 1 nitroglycerin tablets on oxprenolol and 5 9 nitroglycerin tablets on placebo This difference is also not clinically significant

Prichard and his associates[10] reported in a double blind study involving six patients with angina pectoris due to coronary artery disease that intravenous propranolol (the average dose used was 38 mg) intravenous sotalol (the average dose used was 50 mg) 60 mg of intravenous oxprenolol and practolol (the average dose used was 153 mg) produced a significant increase in duration of exercise until the onset of angina in comparison with physiological saline during the first exercise period During the second exercise period propranolol and practolol but neither oxprenolol nor

The medical treatment of angina pectoris VII. Newer beta-adrenergic blockers as antianginal drugs

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Beta adrenergic blocking drugs have been advocated for the treatment of angina pectoris We[1] have previously discussed the efficacy of propranolol as an antianginal agent Newer beta adrenergic blocking drugs such as alprenolol oxprenolol sotalol and practolol have been advocated as effective antianginal drugs which have a less negative inotropic effect on the myocardium than does propranolol However Mitchell and his associates found that equally active doses of propranolol alprenolol, sotalol and practolol displayed equivalent intrinsic negative inotropic activity, and Burgin[3] reported that oxprenolol has cardiodepressant activity which does not differ from propranolol Practolol has also been demonstrated to be a cardioselective beta adrenergic blocking drug The following discussion will critically analyze the efficacy of these newer beta adrenergic blocking drugs as antianginal agents

Wasserman and his associates[4] administered alprenolol 160 mg to 400 mg daily and placebo to nine patients with angina pectoris due to coronary artery disease in a double blind crossover study Eight of their nine patients had angina more frequently on alprenolol than on placebo However, 16 anginal episodes per week per patient on alprenolol in comparison with 13 anginal episodes per week per patient on placebo does not represent any significant clinical difference The mean exercise time until angina pectoris caused their nine patients to stop or slow down was also not significantly different, whether the patient were receiving alprenolol or placebo

Bjorntorp[5] reported in a double blind study that alprenolol administered in a dose of 200 mg to 400 mg daily to 15 patients with angina pectoris due to coronary artery disease was significantly better than placebo in reducing anginal attacks and nitroglycerin consumption Five patients were eliminated from his analysis because they had less than two anginal episodes per week on both placebo and alprenolol If one analyzes his data, one finds that there were 40 anginal episodes per week for eight patients on alprenolol or 5 0 anginal episodes per week per patient on alprenolol and 50 anginal episodes per

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daily and was significantly increased over placebo b 40 per cent in 12 patients who were taking practolol 800 mg daily There was no significant difference in ST segment depression at the onset of anginal pain in 10 patients who were receiving practolol 400 mg daily in comparison with placebo There was a significant reduction in ischemic ST segment depression at the onset of anginal pain in 12 patients from 1 2 mm on placebo to 0 8 mm on practolol 800 mg daily

We feel that these newer beta adrenergic blocking drugs should not be used as antianginal agents in patients with mild angina pectoris congestive failure a recent myocardial infarction poor myocardial contractility significant aortic or mitral valvular disease sinus bradycardia greater than first degree A V block or in patients who are receiving adrenergic augmenting psychotropic drugs or who are prone to develop hypoglycemia In addition oxprenolol sotalol and alprenolol should be avoided in patients with regional vascular insufficiency chronic obstructive lung disease a history of bronchial asthma or with allergic rhinitis during the pollen season

We also recommend that the newer beta adrenergic blocking drugs should be limited as antianginal agents to patients who have severe angina pectoris refractory to other medical management As these beta adrenergic blocking drugs may be helpful to some patients with severe angina pectoris due to coronary artery disease and harmful to other patients these patients should have exercise performance studies and exercise electrocardiograms (ECG s) before and during treatment If the exercise performance deteriorates on the beta adrenergic blocking drug or if the exercise ECG reveals increased ischemic ST segment depression on the drug this drug should then be discontinued and the clinical situation reevaluated Finally it should also be mentioned that the question of carcinogenicity in mice has been raised with practolol by the Food and Drug Administration

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sotalol produced a significant increase in exercise performance until the onset of angina in comparison with saline

Toubes and his associates[11] reported in a double blind crossover trial that sotalol administered in doses of 80 mg daily, 160 mg daily, 320 mg daily, 640 mg daily, and 1 280 mg daily to nine patients with angina pectoris due to coronary artery disease did not cause any significant reduction in the frequency of anginal pain in comparison with placebo therapy The number of anginal attacks was insignificantly greater on the 80 mg and 640 mg daily doses of sotalol than on placebo The mean number of nitroglycerin tablets consumed per week was not reduced on any dose of sotalol to 50 per cent or less of those consumed during the corresponding placebo period

Sandler and Clayton[1] administered in a double blind study 400 mg to 1 200 mg daily of practolol and placebo to 15 patients with angina pectoris due to coronary artery disease The dose of practolol administration was decided by initial open titration in individual patients The mean number of anginal attacks per week was 9 1 on practolol and 8 3 on placebo The mean number of nitroglycerin tablets consumed per week was 35 0 on practolol and 25 3 on placebo These differences are not statistically significant Nine of their 15 patients (60 per cent) developed angina pectoris during an exercise tolerance test while taking practolol whereas 8 of their 15 patients (53 per cent) developed angina pectoris during an exercise tolerance test while taking placebo These results are not significantly different There was a significant decrease in the mean amount of ST segment depression in the radiocardiogram of their patients during exercise from 1 0 mm on placebo to 0 67 mm on practolol However, the duration of ST segment depression in the radiocardiogram during exercise was increased from 233 seconds on placebo to 265 seconds on practolol There was no significant difference in the amount of ST segment depression after exercise or in the duration of ST segment depression after exercise whether their patients were receiving practolol or placebo Practolol a cardioselective beta adrenergic blocking drug was also found in this study to exert no significant effect on the 1 second forced expiratory volume and the forced mid expiratory flow in their 15 patients

Frick and Katila[13] administered in a double blind study practolol 200 mg daily for one month to seven patients with angina pectoris due to coronary artery disease and placebo for one month to seven different patients with angina pectoris due to coronary artery disease After one month of therapy the mean number of anginal attacks per week decreased from 7 0 in the control period to 4 3 in the patients on placebo and from 17 0 in the control period to 10 3 in the patients on practolol These results show no significant difference between practolol 200 mg daily and placebo in the reduction of anginal attacks Practolol 200 mg daily also produced no significant difference in exercise performance or in maximal ST segment depression measured during and after exercise in comparison with placebo

After analyzing the above results Frick and Katila[13] resumed their study by giving placebo for 2 weeks to 10 patients who were willing to continue in their study and practolol 300 mg daily for the subsequent 2 weeks The mean number of anginal attacks per week in their 10 patients was 6 6 while taking placebo and 7 1 while taking practolol 300 mg daily There was also no significant difference in maximal ST segment depression measured during and after exercise whether their patients were receiving practolol 300 mg daily or placebo There was a significant mean improvement in exercise performance of 21 per cent in their patients on practolol compared to placebo in this study which was not double blind

Sowton and his associates[14] found in a double blind crossover study involving 17 patients with angina pectoris due to coronary artery disease that the consumption of nitroglycerin tablets was not significantly different whether the patients were receiving practolol 400 mg daily practolol 800 mg daily or placebo Their patients did not significantly prefer taking practolol 400 mg daily or 800 mg daily in comparison with placebo The total work performed before angina developed was significantly increased over placebo by 32 per cent in 11 patients who were taking practolol 400 mg

incidence of late emboli Atrial fibrillations of recent onset often can be converted to normal sinus rhythm six to eight weeks after surgery using drugs or electric counter shock. McCarthy and associates obtained defibrillation in 52 patients following mitral valve surgery but only ten of them remained in normal sinus rhythm for one year and five until the second year In a study of seven patients with malfunctioning mitral prostheses Roberts and Morrow[4] found prompt development of large thrombi in the left atrium. Obstruction to satisfactory performance of the prosthetic valves resulted from the impingement of the muscular ventricular septum

Continued research on measures to decrease the incidence of thromboembolism is indicated Improvements in the design of the valve and long term anticoagulation are the most important steps presently adopted to achieve this goal An ideal valve should not be a nidus for thrombus formation and should preferably have central flow with little resistance to the emptying of the left atrium during rest and exercise Until such a prosthesis is available as well as persistent atrial fibrillation is uncontrollable after cardiac surgery routine exclusion of the left atrial appendage should be entertained as a simple additional step worthy of consideration. A random study will be necessary to prove or disprove the efficacy of this concept. In the author opinion a double blind study is not indicated in view of the benign and simple nature of this additional step taken during surgery compared to the price of serious or fatal complications of emboli originating from the left atrial appendage in some patients

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Modified orifice equation for the calculation of mitral valve area

Since 1951 the routine evaluation of valvular stenosis in the catheterization laboratory has included a calculation of orifice size Based on hydraulic principles Gorlin and Gorlin[1] derived the orifice equation

$$\text{area} = \frac{\text{flow}}{44.5\, C \sqrt{\text{grad}}}$$

where C is an empirical constant. To calculate the mitral valve area (MVA) one must therefore measure both the gradient and flow across the valve When the orifice equation was initially derived only right-sided cardiac catheterization procedures were available The gradient therefore could not be directly measured Pulmonary capillary wedge pressure (PC) was used as an estimate of the left atrial pressure. Mean left ventricular (LV) diastolic pressure was assumed to be 5 and the gradient was calculated as

$$\text{PC wedge pressure} - 5$$

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With the introduction of transseptal and retrograde arterial techniques it became routine to measure the pressure difference across the MV directly The flow term of the orifice equation was also in part calculated indirectly Flow across the MV takes place only during the diastolic phase of the cardiac cycle and therefore can be defined as

$$\text{flow} = \frac{CO}{(HR)\,(Dfp)}$$

where CO = cardiac output, HR = *heart rate* and Dfp = diastolic filling period

The product of HR and Dfp therefore defines that portion of a minute occupied by diastole Because of the unavailability of LV pressure tracings Dfp was initially calculated from the brachial arterial tracing The period of diastole per beat was measured from the beginning of the dicrotic notch to the beginning of the upstroke of the next pressure pulse. This method of calculating Dfp includes the isometric contraction and relaxation phases of the cardiac cycle as pointed out in the original work and therefore probably overestimates the time for flow

Left atrial appendage and valve replacement

A decade has passed since the advent of total prosthetic replacement of cardiac valves for clinical use. There is little doubt concerning the improvement in quality and quantity of life that patients suffering from valvular heart disease have obtained because of valve replacements. Modifications in the design of valves, technique of implantation, and postoperative care have undergone frequent changes resulting in all time low rates of operative mortality, postoperative morbidity, and late complications.[illegible] Thromboembolism has been the most frequent late complication, whether the valve was repaired or replaced and whether or not anticoagulants were used. Most of us have accepted the frequency of emboli from artificial valves as an inherent problem with emphasis on the design of the prostheses and routine anticoagulation. Wherever feasible, preservation of the patients' own valves by plastic procedures or homograft replacement of the valves has been adopted to overcome the thromboembolic complication. During the past two years the author routinely has ligated the atrial appendage in all patients undergoing mitral valve surgery in an attempt to see if there is a change in the incidence of thromboembolism. This concept is indicated in mitral valve surgery when a right sided or superior approach to the mitral valve is used. The purpose of this communication is to stimulate an interest in this concept and to obtain the reaction of other surgeons with the opportunity to operate on and follow up a larger volume of such patients.

Almost all the patients with rheumatic mitral valve disease have involvement of the atrial appendage by the rheumatic process or by simple dilatation with or without associated fibrillation. Stenosis and insufficiency of the mitral valve result in hypertrophy and enlargement of the entire atrium with changes in the pulmonary vasculature. These changes seldom return to completely normal levels with repair or replacement of the valves. Significant gradients develop across the mitral valve prosthesis in some patients, particularly with exercise despite a normal gradient across the valve at the time of implantation. Myocardial insufficiency due to coronary artery disease, rheumatic pancarditis, or loss of chordal attachments may be seen in many patients who undergo valve replacements. The mitral valve, whether it be normal or artificial, opens by a passive phenomenon because of a sudden drop in the left ventricular pressure during diastole and a simultaneous rise in the left atrial pressure. Therefore, factors such as myocardial insufficiency or gradient across the valve may predispose to thrombus formation in addition to the source of an intracardiac prosthesis. The presence of an intracardiac prosthesis is the most well recognized and frequent source of thromboemboli among patients subjected to valve replacement.

Cardiac arrhythmias, especially atrial fibrillation, stasis, and infection are other factors responsible for the development of thrombus and embolization. Peripheral emboli in patients with atrial fibrillation are frequently seen and generally accepted as originating in the atrium. This need not be associated with mitral valve disease or intracardiac prosthesis. When thrombus is encountered, it again is most often in the appendage of the left atrium. Although the primary source of emboli is the prosthetic valve itself in patients with mitral valve replacement, the left atrial appendage should be considered as the next most likely source. When the mitral valve is repaired or replaced from the right side through the interatrial groove or through the atrium between the superior vena cava and ascending aorta, the appendage is usually left intact. Delayed air emboli by the sequestrated air in the appendage have been reported also.[illegible] Small residual thrombi are common in the appendage after removal of the bulk of the thrombus during the operation. Meticulous removal of the thrombus from the appendage is time consuming and often leaves a raw surface on the endocardium. Therefore, I would like to advocate routine exclusion of the entire left atrial appendage at the time of surgery on the mitral valve or during any cardiac surgery on a patient with chronic atrial fibrillation. A curved vascular clamp is applied across the base of the left atrial appendage and it is ligated by using a heavy suture. Purse-string suturing or amputation of the appendage with closure is an alternative measure but is unnecessary.

In a review of 1,200 patients with mitral valve disease, Bailey and associates[1] found thrombosis of the left atrium in 30 per cent of the patients. Among the patients with left atrial thrombus, 53 per cent had persistent atrial fibrillation. Madden and associates[2] have reported routine exclusion of the left atrial appendage during mitral valve operations. In their study they found that 26 per cent of the 66 patients with atrial fibrillation had emboli in contrast to a 10 per cent incidence among the 62 patients with normal sinus rhythm. They operated upon 16 patients with clotted left atria and saw a 33 per cent incidence of late emboli while 112 patients without left atrial clots had only a 16 per cent

had been replaced In 59 per cent the energy requirement for reversion was 50 w sec or less and in 93 per cent it was 100 w sec or less While the energy level was nearly the same for those with mitral and aortic prostheses it was significantly higher when both valves had been replaced

Of the 11 patients who failed to revert five were in biventricular failure four had atrial fibrillation for more than two years and two showed evidence of digitalis intoxication at the time of cardioversion Four patients had recurrence of atrial fibrillation within 24 hour after reversion All had been in frank congestive heart failure at the time of the procedure Cardioversion was accomplished as an emergency measure in the hope of reversing the intractable heart failure

In order to evaluate the effects of the prosthetic valve in the case of cardioversion upon ensuing complication the 74 patient with mitral valve replacement were compared to 58 who had had merely mitral valvuloplasty Both groups had a similar age distribution a similar duration of arrhythmia, and were subjected to cardioversion during the same time period however there was a larger proportion of female patient among those who

Table I Success rate of cardioversion and energy requirements in 102 patients with valve prosthesis

Valve replacement	No of patients	Success (%)	Mean energy (w sec)
Mitral	74	90 5	77
Aortic	15	86 6	73
Both	13	84 6	109

$P < 0.01$

underwent mitral valvuloplasty i.e. 79 4 per cent as compared to 56 per cent among those with mitral valve replacement. The success rate as well as energy requirement for cardioversion (Table II) was similar in both groups All four patients who failed to revert after mitral valvuloplasty had been in atrial fibrillation for a period of more than nine years

Arrhythmias following cardioversion were observed in 19 of those having had mitral valve replacement and in 21 of those with valvuloplasty These consisted predominantly of ectopic beats of atrial junctional or ventricular origin. The arrhythmias were transient usually disappearing within one minute No major arrhythmias were encountered immediately after cardioversion in any of these patients This is of interest since in only four patients were digitalis drugs discontinued prior to the cardioversion. The absence of significant arrhythmias is accounted for by the titration of energy for reversion thus utilizing in each patient the lowest discharge level necessary for restoring a sinus mechanism[1]

Two major late complications were encountered one in each of these groups A 53 year-old woman was cardioverted with 59 w sec to sinus rhythm three weeks following mitral valve replacement The reversion was uncomplicated She was receiving quinidine gluconate in a dose of 1 0 Gm daily Twenty four hours later she developed ventricular fibrillation from which she was promptly reverted The second patient a 58-year old woman was cardioverted following mitral valvuloplasty Six days after reversion she sustained a pulmonary embolism. At the time of this complication she was receiving adequate anticoagulant therapy She had an uneventful recovery and remained in sinus rhythm

Cardioversion is the easiest and most direct method available for reverting a number of arrhythmias[8] This report indicates that replacement of the mitral or aortic valve does not diminish the

Table II Energies for successful cardioversion of patients with mitral valve replacement as compared to those with mitral valvuloplasty

	Energies (w sec)							Total no of patients
		10	25	50	100	200	300	
Mitral valve replacement								
No	1	1	4	35	21	3	2	67
Per cent	1 5	3 0	9 0	61 ?	9? 5	97	100	
Mitral valvuloplasty								
No	0	1	4	31	15	?	1	54
Per cent	0	1 9	9 3	66 6	94 0	98 1	100	

*Cumulative percentage

across the MV However the empirical constant which was derived by comparing the calculated valve area with that measured at the time of autopsy corrects for this systematic error Using the derived constant for the MV of 0 7 the orifice equation becomes

$$\text{MVA} = \frac{\text{CO}}{(\text{HR})\ (\text{Dfp})\ (31)\ (\sqrt{\text{LC LV diastolic mean}})}$$

A recent publication[3] has advocated deriving diastolic filling period (Dfp') as the duration of the diastolic gradient measured directly from the LV vs PC pressure tracing However despite this change the authors have continued to use the same numerical constant of 31 To allow the orifice equation to be employed with the directly measured Dfp' the numerical constant has been recalculated by reviewing 16 cases of mitral stenosis evaluated in the catheterization laboratory All patients had rheumatic heart disease but only ten had isolated MV disease MVA ranged from 0 5 to 2 2 sq cm One patient also had coronary artery disease Though most patients had some degree of mitral regurgitation for the purpose of the calculation of relative time periods it was assumed that no regurgitation was present All patients were in normal sinus rhythm

Pressure recordings were carefully chosen so that only brachial artery and LV PC traces during the same physiologic state and at identical heart rates were compared Two of the 16 patients had pressure recordings made also during the exercise state The MVA was calculated using the numerical constant 31 as originally proposed[1] and the Dfp measured from the brachial artery pressure trace and averaged for five consecutive cardiac cycles Assuming the result to be the MVA the orifice equation was then rearranged and solved for the numerical constant this time using as diastolic filling period the directly measured Dfp' averaged for five cycles When calculated in this fashion the average *numerical constant* is 37 9 Therefore when using the directly measured Dfp' the orifice equation for calculation of a stenotic mitral valve area should be revised

$$\text{MVA} = \frac{\text{CO}}{(\text{HR})\ (\text{Dfp}')\ (37\ 9)\ (\sqrt{\text{grad}})}$$

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Cardioversion of atrial fibrillation after valve replacement*

Atrial fibrillation affects cardiac performance adversely The more diseased the heart the more important is the atrial contribution made possible by a sinus mechanism The hazard of atrial fibrillation stems largely from the predisposition to thromboembolism which is observed in approximately 30 per cent of those harboring this arrhythmia Sinus rhythm is the best protection against embolic complications Three interrelated problems however need to be considered before attempting reversion of atrial fibrillation to a normal rhythm (1) the likelihood of successful cardioversion (2) the risks entailed by this procedure and (3) the persistence of a normal mechanism.

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The chance of long term maintenance of sinus rhythm after reversion has been improved by prosthetic valve replacement which frequently restore a nearly normal hemodynamic state and by the tendency to operate earlier in the course of the disease A key factor in determining recurrence is the duration of atrial fibrillation prior to reversion[1] With earlier operation the atrial fibrillation is of lesser duration To date little information is available on the success and hazards of cardioversion when employed in patients following valve replacement[2]

We have reviewed our experience involving 850 cardioversions in patients with atrial fibrillations Of this number 102 had prosthetic replacements of the mitral or aortic valves or both (Table I) Cardioversion was successful in restoring sinus rhythm in 91 (89 2 per cent) The success rate was the same for patients with mitral and aortic valve prosthesis and only somewhat less when both valves

Letters to the Editor

Friedreich s ataxia and myocardiopathies

To the Editor

I read the article on Friedreich s ataxia associated with idiopathic hypertrophic subaortic stenosis by Ruschhaupt Thilenius and Ca sel in the July issue of the JOURNAL (AM HEART J 84 95 1972) with great inter st. In the addendum to the article it states that After this paper had been accepted for publication a first and sin le case report of hypertrophic obstructive cardiomyopathy as ociated with Friedreich s ataxia has appe ired in the *American Journal of Cardiology* 27 436 1971

In fact as we pointed out subsequently in a letter to the editor of the *American Journal of Ca diology* (28 496 1971) we published the first case allud ng to thi as ociation in the *American Journal of the Medical Sciences* (260 279 1970) I am happy to see further docum ntation of this association

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Muscular subaortic stenosis and Friedreich s ataxia

Letter to the Editor

We have been much interested and quite astonished by the article concerning the association of Friedreich s ataxia with hypertrophic subaortic stenosis (H S S) written by Ruschhaupt Thilenius and Cassels in your July 1972 issue (AM HEART J 84 95 1972)

The authors specify that their reported case is the second published so far the first one having been reported by J Gach and associates in Vol 27 1971 of the American Journal of Cardiology With all due respect to the authors who have presumably reviewed the literature on the subject it appears to us opportune to bring forward the following remarks!

The first case of H S S associated with Friedreich s ataxia was reported by Soul e and colleagues in Maladie cardio vasculaire Vol 6 1966 This case however had not been documented by left ventriculography We would have been very satisfied to see the left ventriculography in the Rusch haupt case report

We have reported in L Union Médicale du Canada Vol 101 March 1972 a similar case which appeared to be the second one published and documented by left ventriculography On the other hand in this paper we reported the association of H S S with Hurler s disease and *osteogenesa imperfecta* The question arises as to whether this is purely accidental or whether this myocardial manifestation is the result of few neurologic and metabolic di orders Further investi ation would point out and clarify the exact relationship between these pathologic associations

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Reply

To the Editor

The above letters to the editor point out that the association of Friedreich s ataxia and idiopathic hypertroph c subaortic stenosis is not as rare as we had thought during the preparation of our manuscript This represents good supportive evidence that the two diseases are indeed related phenomena and not just fortuitous combinations

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success rate of cardioversion does not increase the effective energy and does not result in an increased incidence of immediate or late complications

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Bernard Lown M D
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Harvard School of Public Health
Cardiology Division
Peter Bent Brigham Hospital
Boston Mass 02115

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The dose of drugs—the right amount

Physicians are always concerned about the proper dosage of drugs to administer to their patients Unless the physician uses a drug regularly he consults the *Physician s Desk Reference* the manufacturer s insert or another type of reference for recommended dosage The drug is then administered accordingly Remember however that it is not possible for any manufacturer to produce a pill that would result in a satisfactory response in every patient It is no more possible for a pharmaceutical manufacturer to produce a universal pill than it is for a sugar refinery to produce a sugar cube that would sweeten the coffee of 200 million Americans just right Imagine asking a strange person or even a physician for the first time to add sugar to your cup of coffee to sweeten it just right for you Taste buds and the taste responses in the brain differ among people Taste is a response people can determine only to their own satisfaction So one adds sugar in the proper or right amount according to his own taste not by reading the insert provided by a sugar manufacturer Surely we know what is essentially average but the amount varies considerably and people have strong feelings about how much sugar they want in their coffee if they are to enjoy it Similarly the amount of a drug administered is determined by the pharmacologic or physiologic response desired in a given individual

This thought introduces another Imagine going to a large restaurant and having a different waiter each time trying to sweeten your coffee just right Only on a chance basis would one of the waiters do so without your assistance But if the same waiter attended you each time he would soon learn to add the right amount of sugar to your coffee and would sweeten it just right The same reasoning applies to doctors and drugs Many patients attend large clinics and hospital services too frequently and unfortunately see different doctors on different visits each doctor having the same difficulties with the adjustment of doses of medicine However if a patient were to see the same doctor each time and if the doctor were knowledgeable the dose of drugs could be made just right for that patient These concepts are readily supported by experience with the use of digitalis and diuretics as well as for all drugs used in the United States of America today

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tions it should also interest those who desire to know about aspects of current thought on the pathogenesis of Atherosclerosis but who have not followed the literature previously There is certainly a need for a symposium on this important subject which is concerned with only new ideas and concepts and is presented by contributors who are engaged in new and different approaches to the pathogenesis of Atherosclerosis This publication is a good one but unfortunately fails to extend our knowledge forward to any significant degree

CARDIAC CLINICOPATHOLOGICAL CONFERENCES OF THE MASSACHUSETTS GENERAL HOSPITAL Edited by Benjamin Castleman M D and Roman W De Sanctis M D Boston 1972 Little Brown & Company 440 pages Price $28 50

This is a compilation of 50 extremely interesting CPC s on cardiac diseases previously published in the New England Journal of Medicine from the Massachusetts General Hospital by Dr Benjamin Castleman The case discussions have had and still have extremely important and interesting *teaching* applications The CPC s are of recent vintage and therefore reflect the present state of medicine at the Massachusetts General Hospital and in the U S A The clinical and pathological discussions are interesting and reflect the process of clinical thinking and logic of outstanding doctors Those who read the CPCs in the New England Journal of Medicine will recall many of the cases This is an excellent publication Dr Castleman has done a fine service to the education of physicians throughout the world with his renowned CPC s

TEXTBOOK OF ELECTROCARDIOGRAPHY By David Littmann M D New York 1972 Harper & Row Publishers Inc. 553 pages Price $22 50

Many books on electrocardiography have been written in recent years this is a good one The approach is sound and the illustrations are clear and well selected The electrocardiograms are particularly sharp and clear This textbook is divided into 7 parts (1) electrophysiology and the normal electrocardiogram (2) hypertrophy strain enlargement and preponderance (3) disorder of conduction (4) coronary heart disease (5) the electrocardiogram in specific disorders (6) the nonspecifically abnormal electrocardiogram and (7) the unknown electrocardiogram There is nothing especially new or different about this book except that it summarizes the author s approach to the subject. The book is not the best for beginners but it is still a good one It should be of most value to those who *have learned* the fundamentals of electrocardiography and wish to review tracings displaying the ECG changes produced by the most common cardiac disease state This is a valuable publication

Books received

BIBLIOTHECA CARDIOLOGICA No 29 CIRCULATORY ASSIST AND BALLISTOCARDIOGRAPHIC STUDIES Proceedings of the 15th Annual Meeting of the Ballistocardiograph Research Society Atlantic City N J 1971 Edited by David H Jackson Basel 1972 S Karger AG 112 pages Price $10 95

BOOK OF THE DESCENDANTS OF DOCTOR BENJAMIN LEE AND DOROTHY GORDON By Gordon Philo Baker M D et al Ventnor N J 1972 Ventnor Publishers 176 pages Price $8 50

CORE TEXTBOOK OF SURGERY Edited by Richard H Egdahl M D John A Mannick M D and Lester F Williams Jr M D New York 1972 Grune & Stratton Inc 484 pages Price $13 50 (Softcover $8 75)

DEVELOPMENT OF THE CHICK HEART By Maria Victoria de la Cruz Simon Munoz Armas and Luis Munoz Castellanos Baltimore and London 1972 The Johns Hopkins University Press 80 pages Price $10 00

EMERGENCY ROOM CARE The Twenty Third Hahnemann Symposium. Edited by Wilbur W Oaks M D and Stanley Spitzer M D under the General Editorship of John H Moyer M D New York 1972 *Grune & Stratton* Inc. 300 pages Price $18 50

YOUR HEART—Complete Information for the Family By *William Likoff* M D Bernard Segal M D and Lawrence Galton Philadelphia and New York 1972 J B Lippincott Company 274 pages Price $6 95

Book reviews

Pathology of the Cerebral Blood Vessels By William E Stehbens M D St Louis 1972 The C V Mosby Company 661 pp

Dr Stehbens has gathered in a single volume extremely important and interesting material concerning the pathology of cerebral blood vessel Cerebrovascular disease is one of the most common and serious problems confronting man today and because of this we are fortunate to have this new book The author discusses the anatomy of the blood vessels of the brain and spinal cord the structure and physiology of the vessels atherosclerosis thrombosis and embolism infarction hematoma hemorrhage aneurysms tumors and other aspects of the diseases of the cerebral blood vessels The discussions are clear the illustrations well selected and the bibliography is good The book is also nicely printed and the illustrations are well reproduced This is not only a good book but an important one that should interest clinicians as much as pathologists

Cardiac Arrhythmias A symposium Edited by Jaol Han M D Ph D Springfield Ill 1972 Charles C Thomas Publisher 301 pp Price $23 50

This series of papers was presented at a symposium on cardiac arrhythmias held during January 1970 at the Albany Medical College The contributors have been interested in their respective subjects for many years and briefly describe their ideas for students learning electrocardiography The thirteen papers include the common clinical problems There is nothing really new in this series of lectures but they should be of considerable value to undergraduate students interns residents and fellows The presentations in the texts and the figures are good This is a good small book on the subject of arrhythmias

Advances in Electrocardiography Edited by Robert C Schlant M D and J Willis Hurst M D New York 1972 Grune & Stratton Inc 464 pp Price $24 75

This is a volume of a series on cardiovascular disease It contains several papers written by different contributors Those who have followed the medical literature will find a great deal of the advances described are not recent even though they are interesting and important This collection of papers involves five main topics—i e general electrophysiology pathophysiology of conduction and abnormal cardiac rhythm pre excitation syndromes hypertrophy and infarction and miscellaneous subjects Some of the presentations are authoritative and the concepts well established whereas others are not The reader never theless will find the 26 presentations to be valuable and worth critical study Vectorcardiography is also included among the presentations This is another interesting book on electrocardiography among the many that have appeared in recent years

Advances in Cardiology vol 7, Long term Prognosis Following Valve Replacement Edited by J H K Vogel Basel 1972 S Karger AG 281 pages Price $27 75

This monograph summarizes the Second Conference on Cardiovascular Disease in Snowmass at Aspen Aspen Colorado held from January 10 through 12 1971 The book is concerned with four major subjects consideration of valve structure long term results with prosthetic valves long term results with valve grafts and clinical considerations of valve replacement This is an important book which should interest all cardiologists and heart surgeons The valves used in valve replacement are far from perfect and certainly do not fully substitute for the natural ones which are known to last and function well for 100 years These many papers indicate some of the many problems remaining in this field of cardiology as well as the outstanding successes This publication includes important prognostic information which should interest all doctors who are contemplating using valve replacement in their patients The symposium must have been an interesting one

The Pathogenesis of Atherosclerosis Edited by R W Wissler Ph D M D and J C Geer M D Baltimore 1972 The Williams & Wilkins Company 262 pages Price $25 00

This volume consists of a group of papers of presentations made at the Symposium on the Pathogenesis of Atherosclerosis held with the annual meeting of the American Association of Pathologists and Bacteriologists The authors of the papers and the participants are essentially the same who participate in most symposia of this type therefore the contributors are well known And as one would have expected the symposium failed to reveal any really new significant idea or findings The presentations were concerned with modern theories natural history risk factors animal models hemodynamic risk factors arterial wall metabolism thrombosis lipoprotein and prevention There is also an appendix to this volume on methods for evaluating myocardial and coronary artery lesions The papers are well written and the illustrations are excellent This book should interest those who did not attend the meeting and who wished to know of the presenta

tion it should also interest those who desire to know about aspects of current thought on the pathogenesis of Atherosclerosis but who have not followed the literature previously There is certainly a need for a symposium on this important subject which is concerned with only new ideas and concepts and is presented by contributors who are engaged in new and different approaches to the pathogenesis of Atherosclerosis This publication is a good one but unfortunately fails to extend our knowledge forward to any significant degree

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Announcements

Symposium on nutrition

The University of Texas Graduate School of Biomedical Sciences at Houston Division of Continuing Education announces the Texas Medical Center s Sympo ium on the Application of Nutrition in the Health Sciences to be conducted in Houston Texas on January 12 and 13 1973

The program will be presented in four parts (1) Anemia—the number one problem in the U S (why–diagno is prevalence therapy and prevention) (2) Diet and chronic disea es—fact vs fad and fallacy (3) Recent advances in nutrition re earch and (4) Preventive and therapeutic nutrition Participating in the symposium will be well known investigators in the field of nutrition.

For further information write The Office of the Dean The Univer ity of Texas Graduate School of Biomedical Sciences at Houston Division of Continuing Education P O Box 20367 Hou ton Texas 77025

American Heart Journal

An international publication for the study of the circulation

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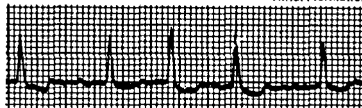
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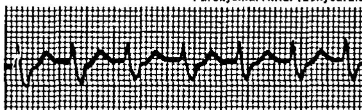
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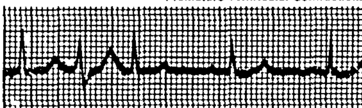
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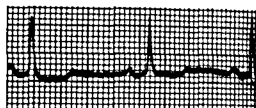
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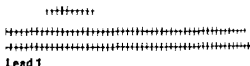
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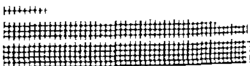
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